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(21) International Application Number: PCT/GB97/02479 (22) International Filing Date: 11 September 1997 (11.09.97) (30) Priority Data: PO 2246 11 September 1996 (11.09.96) AU (71) Applicant (for all designated States except US): AMRAD OPERATIONS PTY. LTD. [AU/AU]; 576 Swan Street, Richmond, VIC 3121 (AU). (71) Applicant (for GB only): DZIEGLEWSKA, Hanna, Eva [GB/GB]; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): HILTON, Douglas, James [AU/AU]; 244 Research Road, Warrandyte, VIC 3113 (AU). NICOLA, Nicos, Antony [AU/AU]; 56 Churchill Avenue, Mont Albert, VIC 3127 (AU). FARLEY, Alison [AU/AU]; 27/9-19 Miller Street, North Fitzroy, VIC 3068 (AU). WILLSON, Tracy [AU/AU]; 26 Fortuna Avenue, North Balwyn, VIC 3104 (AU). ZHANG, Jian-Guo [CN/AU]; 3 Karri Crescent, Hoppers Crossing, VIC 3029 (AU). ALEXANDER, Warren [AU/AU]; 13 Park Street, Moonee Ponds, VIC 3039 (AU). RAKAR, Steven [AU/AU]; 26 Riverside		Avenue, Avondale Heights, VIC 3034 (AU). FABRI, Louis [AU/AU]; 8 Laver Court, Mill Park, VIC 3082 (AU). KOJIMA, Tetsuo [JP/JP]; 1-8-1-302 Minami-Rokugou, Ota-ku, Tokyo 144 (JP). MAEDA, Masatsugu [JP/JP]; 1-6-2-606 Kasuga, Tsukuba, Ibaraki 305 (JP). KIKUCHI, Yasufumi [JP/JP]; 1-29-5-110 Komatsu, Tsuchiura, Ibaraki 300 (JP). NASH, Andrew [AU/AU]; 24 Green Street, Northcote, VIC 3070 (AU). (74) Agents: DZIEGLEWSKA, Hanna, Eva et al.; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: A NOVEL HAEMOPOIETIN RECEPTOR AND GENETIC SEQUENCES ENCODING SAME (57) Abstract <p>The present invention relates generally to a novel haemopoietin receptor or derivatives thereof and to genetic sequences encoding same. Interaction between the novel receptor of the present invention and a cytokine ligand facilitates proliferation, differentiation and survival of a wide variety of cells. The novel receptor and its derivatives and the genetic sequences encoding same of the present invention are useful in the development of a wide range of agonists, antagonists, therapeutics and diagnostic reagents based on ligand interaction with its receptor.</p>		

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A NOVEL HAEMOPOIETIN RECEPTOR AND GENETIC
SEQUENCES ENCODING SAME

5 The present invention relates generally to a novel
haemopoietin receptor or derivatives thereof and to
genetic sequences encoding same. Interaction between
the novel receptor of the present invention and a ligand
facilitates proliferation, differentiation and survival
of a wide variety of cells. The novel receptor and its
10 derivatives and the genetic sequences encoding same of
the present invention are useful in the development of a
wide range of agonists, antagonists, therapeutics and
diagnostic reagents based on ligand interaction with its
receptor.

15 Bibliographic details of the publications numerically
referred to in this specification are collected at the
end of the description. Sequence Identity Numbers (SEQ
ID NOs.) for the nucleotide and amino acid sequences
20 referred to in the specification are defined following
the bibliography.

Throughout this specification and the claims which
follow, unless the context requires otherwise, the word
25 "comprise", or variations such as "comprises" or
"comprising", will be understood to imply the inclusion
of a stated integer or group of integers but not the
exclusion of any other integer or group of integers.

30 The rapidly increasing sophistication of recombinant DNA
techniques is greatly facilitating research into the
medical and allied health fields. Cytokine research is
of particular importance, especially as these molecules
regulate the proliferation, differentiation and function
35 of a wide variety of cells. Administration of
recombinant cytokines or regulating cytokine function
and/or synthesis is becoming increasingly the focus of

medical research into the treatment of a range of disease conditions.

5 Despite the discovery of a range of cytokines and other secreted regulators of cell function, comparatively few cytokines are directly used or targeted in therapeutic regimens. One reason for this is the pleiotropic nature of many cytokines. For example, interleukin (IL)-11 is a functionally pleiotropic molecule (1,2), initially
10 characterized by its ability to stimulate proliferation of the IL-6-dependent plasmacytoma cell line, T11 65 (3). Other biological actions of IL-11 include induction of multipotential haemopoietin progenitor cell proliferation (4,5,6), enhancement of megakaryocyte and
15 platelet formation (7,8,9,10), stimulation of acute phase protein synthesis (11) and inhibition of adipocyte lipoprotein lipase activity (12, 13).

Other important cytokines in the IL-11 group include IL-
20 6, leukaemia inhibitory factor (LIF), oncostatin M (OSM) and CNTF. All these cytokines exhibit pleiotropic properties with significant activities in proliferation, differentiation and survival of cells. Members of the haemopoietin receptor family are defined by the presence
25 of a conserved amino acid domain in their extracellular region. However, despite the low level of amino acid sequence conservation between other haemopoietin receptor domains of different receptors, they are all predicted to assume a similar tertiary structure,
30 centred around two fibronectin-type III repeats (18,19).

The size of the haemopoietin receptor family has now become extensive and includes the cell surface receptors for many cytokines including interleukin-2 (IL-2), IL-3,
35 IL-4, IL-5, IL-6, IL-7, IL-9, IL-11, IL-12, IL-13, IL-15, granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage-CSF (GM-CSF), erythropoietin,

thrombopoietin, leptin, leukaemia inhibitory factor, oncostatin-M, ciliary neurotrophic factor, cardiotrophin, growth hormone and prolactin. Although most of the members of the haemopoietin receptor family act as classic cell surface receptors, binding their cognate ligand at the cell surface and initiating intracellular signal transduction, some receptors are also produced in naturally occurring soluble forms. These soluble receptors can either act as cytokine antagonists, by binding to cytokines and inhibiting productive interactions with cell surface receptors (eg LIF binding protein; (20) or as agonists, binding to cytokine and potentiating interaction with cell surface receptor components (eg soluble interleukin-6 receptor a-chain; (21)). Still other members of the family appear to be produced only as secreted proteins, with no evidence of a cell surface form. In this regard, the IL-12 p40 subunit is a useful example. The cytokine IL-12 is secreted as a heterodimer composed of a p35 subunit which shows similarity to cytokines such as IL-6 (22) and a p40 subunit which shares similarity with the IL-6 receptor a-chain (23). In this case the soluble receptor acts as part of the cytokine itself and essential to formation of an active protein. In addition to acting as cytokines (eg IL-12p40), cytokine agonists (eg IL-6 receptor a-chain) or cytokine antagonists (LIF binding protein), members of the haemopoietin receptor have been useful in the discovery of small molecule cytokine mimetics. For example, the discovery of peptide mimetics of two commercially valuable cytokines, erythropoietin and thrombopoietin, centred on the selection of peptides capable of binding to soluble versions of the erythropoietin and thrombopoietin receptors (24,25). Due to the importance and multifactorial nature of these cytokines, there is a need to identify receptors, including both cell bound and soluble, for pleiotropic cytokines. Identification

of such receptors permits the identification of pleiotropic cytokines and the development of a range of therapeutic and diagnostic agents.

5 Accordingly, one aspect of the present invention relates to a nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding a novel haemopoietin receptor or a derivative thereof.

10

More particularly, the present invention provides a nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding a novel haemopoietin receptor or a derivative thereof having the motif:

15

Trp Ser Xaa Trp Ser [SEQ ID NO:1],
wherein Xaa is any amino acid and is preferably Asp or Glu.

20

Even more particularly, the present invention is directed to a nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding a novel haemopoietin receptor or a derivative thereof, said receptor comprising the motif:

25

Trp Ser Xaa Trp Ser [SEQ ID NO:1]

wherein Xaa is any amino acid and is preferably Asp or Glu, said nucleic acid molecule is identifiable by hybridisation to said molecule under low stringency conditions at 42EC with

30

5N (A/G)CTCCA(A/G)TC(A/G)CTCCA 3N [SEQ ID NO:7]

and

5N (A/G)CTCCA(C/T)TC(A/G)CTCCA 3N [SEQ ID NO:8].

35

Still more particularly, the present invention provides an isolated nucleic acid molecule comprising a sequence

of nucleotides substantially as set forth in SEQ ID
NO:12 or a nucleotide sequence having at least 60%
similarity to the nucleotide sequence set forth in SEQ
ID NO:12 or a nucleotide sequence capable of hybridising
5 thereto under low stringency conditions at 42EC and
wherein said nucleotide sequence encodes a novel
haemopoietin receptor or a derivative thereof.

10 In a related embodiment, the present invention provides
an isolated nucleic acid molecule comprising a sequence
of nucleotides substantially as set forth in SEQ ID
NO:14 or a nucleotide sequence having at least 60%
similarity to the nucleotide sequence set forth in SEQ
ID NO:14 or a nucleotide sequence capable of hybridising
15 thereto under low stringency conditions at 42EC and
wherein said nucleotide sequence encodes a novel
haemopoietin receptor or a derivative thereof.

20 In another related embodiment, the present invention
provides an isolated nucleic acid molecule comprising a
sequence of nucleotides substantially as set forth in
SEQ ID NO:16 or a nucleotide sequence having at least
60% similarity to the nucleotide sequence set forth in
SEQ ID NO:16 or a nucleotide sequence capable of
25 hybridising thereto under low stringency conditions at
42EC and wherein said nucleotide sequence encodes a
novel haemopoietin receptor or a derivative thereof.

30 In a further related embodiment, the present invention
provides an isolated nucleic acid molecule comprising a
sequence of nucleotides substantially as set forth in
SEQ ID NO:18 or a nucleotide sequence having at least
60% similarity to the nucleotide sequence set forth in
SEQ ID NO:18 or a nucleotide sequence capable of
35 hybridising thereto under low stringency conditions at
42EC and wherein said nucleotide sequence encodes a
novel haemopoietin receptor or a derivative thereof.

In yet a further related embodiment, the present invention provides an isolated nucleic acid molecule comprising a sequence of nucleotides substantially as set forth in SEQ ID NO:24 or a nucleotide sequence
5 having at least 60% similarity to the nucleotide sequence set forth in SEQ ID NO:24 or a nucleotide sequence capable of hybridising thereto under low stringency conditions at 42EC and wherein said nucleotide sequence encodes a novel haemopoietin
10 receptor or a derivative thereof.

Still yet a further embodiment of the present invention is directed to a sequence of nucleotides substantially as set forth in SEQ ID NO:28 or a nucleotide sequence
15 having at least 60% similarity to the nucleotide sequence set forth in SEQ ID NO:28 or a nucleotide sequence capable of hybridising thereto under low stringency conditions at 42EC and wherein said nucleotide sequence encodes a novel haemopoietin
20 receptor or a derivative thereof.

In still yet another embodiment, the present invention provides an isolated nucleic acid molecule comprising a sequence of nucleotides substantially set forth in SEQ
25 ID NO:38 or a nucleotide sequence having at least 60% similarity to the nucleotide sequence set forth in SEQ ID NO:38 or a nucleotide sequence capable of hybridising thereto under low stringency conditions at 42EC and wherein said nucleotide sequence encodes a novel
30 haemopoietin receptor or a derivative thereof.

The term "receptor" is used in its broadest sense and includes any molecule capable of binding, associating or otherwise interacting with a ligand. Generally, the
35 interaction will have a signalling effect although the present invention is not necessarily so limited. For example, the "receptor" may be in soluble form, often

referred to as a cytokine binding protein. A receptor may be deemed a receptor notwithstanding that its ligand or ligands has or have not been identified.

5 Preferably, the novel receptor is derived from a mammal or a species of bird. Particularly, preferred mammals include humans, primates, laboratory test animals (e.g. mice, rats, rabbits, guinea pigs), livestock animals (e.g. sheep, horses, pigs, cows), companion animals
10 (e.g. dogs, cats) or captive wild animals (e.g. deer, foxes, kangaroos). Although the present invention is exemplified with respect to mice, the scope of the subject invention extends to all animals and in particular humans.

15

The present invention is predicated in part on an ability to identify members of the haemopoietin receptor family with limited sequence similarity. Based on this approach, a genetic sequence has been identified in
20 accordance with the present invention which encodes a novel receptor. The expressed genetic sequence is referred to herein as "NR6". Different forms of NR6 are referred to as, for example, NR6.1, NR6.2 and NR6.3. The nucleotide and corresponding amino acid sequences
25 for these molecules are represented in SEQ ID NOS:12, 14 and 16, respectively.

Preferred human and murine nucleic acid sequences for NR6 or its derivatives include sequences from brain,
30 liver, kidney, neonatal, embryonic, cancer or tumour-derived tissues.

Reference herein to a low stringency at 42EC includes and encompasses from at least about 1% v/v to at least
35 about 15% v/v formamide and from at least about 1M to at least about 2M salt for hybridisation, and at least about 1M to at least about 2M salt for washing

conditions. Alternative stringency conditions may be applied where necessary, such as medium stringency, which includes and encompasses from at least about 16% v/v to at least about 30% v/v formamide and from at least about 0.5M to at least about 0.9M salt for hybridisation, and at least about 0.5M to at least about 0.9M salt for washing conditions, or high stringency, which includes and encompasses from at least about 31% v/v to at least about 50% v/v formamide and from at least about 0.01M to at least about 0.15M salt for hybridisation, and at least about 0.01M to at least about 0.15M salt for washing conditions.

The nucleic acid molecules contemplated by the present invention are generally in isolated form and are preferably cDNA or genomic DNA molecules. In a particularly preferred embodiment, the nucleic acid molecules are in vectors and most preferably expression vectors to enable expression in a suitable host cell. Particularly useful host cells include prokaryotic cells, mammalian cells, yeast cells and insect cells. The cells may also be in the form of a cell line.

Accordingly, another aspect of the present invention provides an expression vector comprising a nucleic acid molecule encoding the novel haemopoietin receptor or a derivative thereof as hereinbefore described, said expression vector capable of expression in a selected host cell.

Another aspect of the present invention contemplates a method for cloning a nucleotide sequence encoding NR6 or a derivative thereof, said method comprising searching a nucleotide data base for a sequence which encodes the amino acid sequence set forth in SEQ ID NO:1, designing one or more oligonucleotide primers based on the nucleotide sequence located in the search, screening a

nucleic acid library with said one or more oligonucleotides and obtaining a clone therefrom which encodes said NR6 or part thereof.

5 Once a novel nucleotide sequence is obtained as indicated above encoding NR6, oligonucleotides may be designed which bind cDNA clones with high stringency. Direct colony hybridisation may be employed or PCR
10 amplification may be used. The use of oligonucleotide primers which bind under conditions of high stringency ensures rapid cloning of a molecule encoding the novel NR6 and less time is required in screening out cloning artefacts. However, depending on the primers used, low or medium stringency conditions may also be employed.

15 Alternatively, a library may be screened directly such as using oligonucleotides set forth in SEQ ID NO:7 or SEQ ID NO:8 or a mixture of both oligonucleotides may be used. In addition, one or more of oligonucleotides
20 defined in SEQ ID NO:2 to 11 may also be used.

Preferably, the nucleic acid library is a cDNA, genomic, cDNA expression or mRNA library.

25 Preferably, the nucleic acid library is a cDNA expression library.

Preferably, the nucleotide data base is of human or murine origin and of brain, liver, kidney, neo-natal
30 tissue, embryonic tissue, tumour or cancer tissue origin.

Preferred percentage similarities to the reference nucleotide sequences include at least about 70%, more
35 preferably at least about 80%, still more preferably at least about 90% and even more preferably at least about 95% or above.

Another aspect of the present invention provides an isolated nucleic acid molecule comprising a sequence of nucleotides encoding a novel haemopoietin receptor or derivative thereof having an amino acid sequence as set forth in SEQ ID NO:13 or having at least about 50% similarity to all or part thereof.

Still yet another aspect of the present invention provides an isolated nucleic acid molecule comprising a sequence of nucleotides encoding a novel haemopoietin receptor or derivative thereof having an amino acid sequence as set forth in SEQ ID NO:15 or having at least about 50% similarity to all or part thereof.

Even yet another aspect of the present invention provides an isolated nucleic acid molecule comprising a sequence of nucleotides encoding a novel haemopoietin receptor or derivative thereof having an amino acid sequence as set forth in SEQ ID NO:17 or having at least about 50% similarity to all or part thereof.

A further aspect of the present invention provides an isolated nucleic acid molecule comprising a sequence of nucleotides encoding a novel haemopoietin receptor or derivative thereof having an amino acid sequence as set forth in SEQ ID NO:19 or having at least about 50% similarity to all or part thereof.

Even yet a another aspect of the present invention provides an isolated nucleic acid molecule comprising a sequence of nucleotides encoding a novel haemopoietin receptor or derivative thereof having an amino acid sequence as set forth in SEQ ID NO:25 or having at least about 50% similarity to all or part thereof.

Another aspect of the present invention provides an isolated nucleic acid molecule comprising a sequence of

nucleotides encoding a novel haemopoietin receptor or derivative thereof having an amino acid sequence as set forth in one or more of SEQ ID NOs:29 or having at least about 50% similarity to all or part thereof.

5

Preferably, the percentage amino acid similarity is at least about 60%, more preferably at least about 70%, even more preferably at least about 80-85% and still even more preferably at least about 90-95% or greater.

10

The NR6 polypeptide contemplated by the present invention includes, therefore, derivatives which are components, parts, fragments, homologues or analogues of the novel haemopoietin receptors which are preferably encoded by all or part of a nucleotide sequences substantially set forth in SEQ ID NO:12 or 14 or 16 or 18 or 25 or 20 or 24 or 28 or 38 or a molecule having at least about 60% nucleotide similarity to all or part thereof or a molecule capable of hybridising to the nucleotide sequence set forth in SEQ ID NO:12 or 14 or 16 or 18 or 20 or 24 or 28 or 38 or a complementary form thereof. The NR6 molecule may be glycosylated or non-glycosylated. When in glycosylated form, the glycosylation may be substantially the same as naturally occurring haemopoietin receptor or may be a modified form of glycosylation. Altered or differential glycosylation states may or may not affect binding activity of the novel receptor.

25

30

The NR6 haemopoietin receptor may be in soluble form or may be expressed on a cell surface or conjugated or fused to a solid support or another molecule.

35

As stated above, the present invention further contemplates a range of derivatives of NR6. Derivatives include fragments, parts, portions, mutants, homologues and analogues of the NR6 polypeptide and corresponding

genetic sequence. Derivatives also include single or multiple amino acid substitutions, deletions and/or additions to NR6 or single or multiple nucleotide substitutions, deletions and/or additions to the genetic sequence encoding NR6. "Additions" to amino acid sequences or nucleotide sequences include fusions with other peptides, polypeptides or proteins or fusions to nucleotide sequences. Reference herein to ANR6" includes reference to all derivatives thereof including functional derivatives or NR6 immunologically interactive derivatives.

Analogues of NR6 contemplated herein include, but are not limited to, modification to side chains, incorporating of unnatural amino acids and/or their derivatives during peptide, polypeptide or protein synthesis and the use of crosslinkers and other methods which impose conformational constraints on the proteinaceous molecule or their analogues.

Examples of side chain modifications contemplated by the present invention include modifications of amino groups such as by reductive alkylation by reaction with an aldehyde followed by reduction with NaBH_4 ; amidination with methylacetimidate; acylation with acetic anhydride; carbamoylation of amino groups with cyanate; trinitrobenzylation of amino groups with 2, 4, 6-trinitrobenzene sulphonic acid (TNBS); acylation of amino groups with succinic anhydride and tetrahydrophthalic anhydride; and pyridoxylation of lysine with pyridoxal-5-phosphate followed by reduction with NaBH_4 .

The guanidine group of arginine residues may be modified by the formation of heterocyclic condensation products with reagents such as 2,3-butanedione, phenylglyoxal and glyoxal.

The carboxyl group may be modified by carbodiimide activation via O-acylisourea formation followed by subsequent derivitisation, for example, to a corresponding amide.

5

Sulphydryl groups may be modified by methods such as carboxymethylation with iodoacetic acid or iodoacetamide; performic acid oxidation to cysteic acid; formation of a mixed disulphides with other thiol compounds; reaction with maleimide, maleic anhydride or other substituted maleimide; formation of mercurial derivatives using 4-chloromercuribenzoate, 4-chloromercuriphenylsulphonic acid, phenylmercury chloride, 2-chloromercuri-4-nitrophenol and other mercurials; carbamoylation with cyanate at alkaline pH.

10

15

20

Tryptophan residues may be modified by, for example, oxidation with N-bromosuccinimide or alkylation of the indole ring with 2-hydroxy-5-nitrobenzyl bromide or sulphenyl halides. Tyrosine residues on the other hand, may be altered by nitration with tetranitromethane to form a 3-nitrotyrosine derivative.

25

Modification of the imidazole ring of a histidine residue may be accomplished by alkylation with iodoacetic acid derivatives or N-carbethoxylation with diethylpyrocarbonate.

30

35

Examples of incorporating unnatural amino acids and derivatives during peptide synthesis include, but are not limited to, use of norleucine, 4-amino butyric acid, 4-amino-3-hydroxy-5-phenylpentanoic acid, 6-aminoheptanoic acid, t-butylglycine, norvaline, phenylglycine, ornithine, sarcosine, 4-amino-3-hydroxy-6-methylheptanoic acid, 2-thienyl alanine and/or D-isomers of amino acids. A list of unnatural amino acid, contemplated herein is shown in Table 1.

These types of modifications may be important to stabilise NR6 if administered to an individual or for use as a diagnostic reagent.

- 5 Crosslinkers can be used, for example, to stabilise 3D conformations, using homo-bifunctional crosslinkers such as the bifunctional imido esters having $(CH_2)_n$ spacer groups with $n=1$ to $n=6$, glutaraldehyde, N-hydroxysuccinimide esters and hetero-bifunctional
- 10 reagents which usually contain an amino-reactive moiety such as N-hydroxysuccinimide and another group specific-reactive moiety such as maleimido or dithio moiety (SH) or carbodiimide (COOH). In addition, peptides can be conformationally constrained by, for example,
- 15 incorporation of C" and N "-methylamino acids, introduction of double bonds between C_α and C_β atoms of amino acids and the formation of cyclic peptides or analogues by introducing covalent bonds such as forming an amide bond between the N and C termini, between two
- 20 side chains or between a side chain and the N or C terminus.

TABLE 1

	Non-conventional amino acid	Code	Non-conventional amino acid	Code
5	aminobutyric acid	Abu	L-N-methylalanine	Nmala
	Amino-"-methylbutyrate	Mgab	L-N-methylarginine	Nmarg
	aminocyclopropane-	Cpro	L-N-methylasparagine	Nmasn
	carboxylate		L-N-methylaspartic acid	Nmasp
10	aminoisobutyric acid	Aib	L-N-methylcysteine	Nmcys
	aminonorbornyl-	Norb	L-N-methylglutamine	Nmgln
	carboxylate		L-N-methylglutamic acid	Nmglu
	cyclohexylalanine		ChexaL-N-methylhistidine	Nmhis
	cyclopentylalanine	Cpen	L-N-methylisoleucine	Nmile
15	D-alanine	Dal	L-N-methylleucine	Nmleu
	D-arginine	Darg	L-N-methyllysine	Nmlys
	D-aspartic acid	Das	L-N-methylmethionine	Nmmet
	D-cysteine	Dcys	L-N-methylnorleucine	Nmnle
	D-glutamine	Dgln	L-N-methylnorvaline	Nmnva
20	D-glutamic acid	Dglu	L-N-methylornithine	Nmorn
	D-histidine	Dhis	L-N-methylphenylalanine	Nmphe
	D-isoleucine	Dile	L-N-methylproline	Nmpro
	D-leucine	Dleu	L-N-methylserine	Nmser
	D-lysine	Dlys	L-N-methylthreonine	Nmthr
25	D-methionine	Dmet	L-N-methyltryptophan	Nmtrp
	D-ornithine	Dorn	L-N-methyltyrosine	Nmtyr
	D-phenylalanine	Dphe	L-N-methylvaline	Nmval
	D-proline	Dpro	L-N-methylethylglycine	Nmetg
	D-serine	Dser	L-N-methyl-t-butylglycine	Nmtbug
30	D-threonine	Dthr	L-norleucine	Nle
	D-tryptophan	Dtrp	L-norvaline	Nva
	D-tyrosine	Dtyr	"-methyl-aminoisobutyrate	Maib
	D-valine	Dval	"-methyl-(-aminobutyrate	Mgab
	D-"-methylalanine	Dmala	"-methylcyclohexylalanine	Mchexa
35	D-"-methylarginine	Dmarg	"-methylcyclopentylalanine	Mcpen
	D-"-methylasparagine	Dmasn	"-methyl-"-naphthylalanine	Manap
	D-"-methylaspartate	Dmasp	"-methylpenicillamine	Mpen

	D- "-methylcysteine	Dmcys	N- (4-aminobutyl)glycine	Nglu
	D- "-methylglutamine	Dmgln	N- (2-aminoethyl)glycine	Naeg
	D- "-methylhistidine	Dmhis	N- (3-aminopropyl)glycine	Norn
	D- "-methylisoleucine	Dmile	N-amino- "-methylbutyrate	Nmaabu
5	D- "-methyllleucine	Dmleu	"-naphthylalanine	Anap
	D- "-methyllysine	Dmlys	N-benzylglycine	Nphe
	D- "-methylmethionine	Dmmet	N- (2-carbamylethyl)glycine	Ngln
	D- "-methylornithine	Dmorn	N- (carbamylmethyl)glycine	Nasn
	D- "-methylphenylalanine	Dmphe	N- (2-carboxyethyl)glycine	Nglu
10	D- "-methylproline	Dmpro	N- (carboxymethyl)glycine	Nasp
	D- "-methylserine	Dmser	N-cyclobutylglycine	Ncbut
	D- "-methylthreonine	Dmthr	N-cycloheptylglycine	Nchep
	D- "-methyltryptophan	Dmtrp	N-cyclohexylglycine	Nchex
	D- "-methyltyrosine	Dmtyr	N-cyclodecylglycine	Ncdec
15	D- "-methylvaline	Dmval	N-cylcododecylglycine	Ncdod
	D-N-methylalanine	Dnmala	N-cyclooctylglycine	Ncoct
	D-N-methylarginine	Dnmarg	N-cyclopropylglycine	Ncpro
	D-N-methylasparagine	Dnmasn	N-cycloundecylglycine	Ncund
	D-N-methylaspartate	Dnmasp	N- (2,2-diphenylethyl)glycine	Nbhm
20	D-N-methylcysteine	Dnmcys	N- (3,3-diphenylpropyl)glycine	Nbhe
	D-N-methylglutamine	Dnmgln	N- (3-guanidinopropyl)glycine	Narg
	D-N-methylglutamate	Dnmglu	N- (1-hydroxyethyl)glycine	Nthr
	D-N-methylhistidine	Dnmhis	N- (hydroxyethyl)glycine	Nser
	D-N-methylisoleucine	Dnmile	N- (imidazolylethyl)glycine	Nhis
25	D-N-methyllleucine	Dnmleu	N- (3-indolylyethyl)glycine	Nhtrp
	D-N-methyllysine	Dnmlys	N-methyl- (-aminobutyrate	Nmgabu
	N-methylcyclohexylalanine	Nmchexa	D-N-methylmethionine	Dnmmet
	D-N-methylornithine	Dnmorn	N-methylcyclopentylalanine	
	NmcpenN-methylglycine	Nala	D-N-methylphenylalanine	Dnmphe
30	N-methylaminoisobutyrate	Nmaib	D-N-methylproline	Dnmpro
	N- (1-methylpropyl)glycine	Nile	D-N-methylserine	Dnmser
	N- (2-methylpropyl)glycine	Nleu	D-N-methylthreonine	Dnmthr
	D-N-methyltryptophan	Dnmtrp	N- (1-methylethyl)glycine	Nval
	D-N-methyltyrosine	Dnmtyr	N-methyla-naphthylalanine	Nmanap
35	D-N-methylvaline	Dnmval	N-methylpenicillamine	Nmpen
	(-aminobutyric acid	Gabu	N- (p-hydroxyphenyl)glycine	Nhtyr
	L- α -butylglycine	Tbug	N- (thiomethyl)glycine	Ncys

	L-ethylglycine	Etg	penicillamine	Pen
	L-homophenylalanine	Hphe	L--methylalanine	Mala
	L--methylarginine	Marg	L--methylassparagine	Masn
	L--methylasspartate	Masp	L--methyl-t-butylglycine	Mtbug
5	L--methylcysteine	Mcys	L-methylethylglycine	Metg
	L--methylglutamine	Mgln	L--methylglutamate	Mglu
	L--methylhistidine	Mhis	L--methylhomophenylalanine	Mhphe
	L--methylisoleucine	Mile	N-(2-methylthioethyl)glycine	Nmet
	L--methyllleucine	Mleu	L--methyllysine	Mlys
10	L--methylmethionine	Mmet	L--methylnorleucine	Mnle
	L--methylnorvaline	Mnva	L--methylornithine	Morn
	L--methylphenylalanine	Mphe	L--methylproline	Mpro
	L--methylserine	Mser	L--methylthreonine	Mthr
	L--methyltryptophan	Mtrp	L--methyltyrosine	Mtyr
15	L--methylvaline	Mval	L-N-methylhomophenylalanine	Nmhph
	N-(N-(2,2-diphenylethyl)	Nnbhm	N-(N-(3,3-diphenylpropyl)	Nnbhe
	carbamylmethyl)glycine		carbamylmethyl)glycine	
	1-carboxy-1-(2,2-diphenyl-	Nmbc	ethylamino) cyclopropane	

20

The present invention further contemplates chemical analogues of NR6 capable of acting as antagonists or agonists of NR6 or which can act as functional analogues of NR6. Chemical analogues may not necessarily be derived from NR6 but may share certain conformational similarities. Alternatively, chemical analogues may be specifically designed to mimic certain physiochemical properties of NR6. Chemical analogues may be chemically synthesised or may be detected following, for example, natural product screening.

30

The identification of NR6 permits the generation of a range of therapeutic molecules capable of modulating expression of NR6 or modulating the activity of NR6. Modulators contemplated by the present invention includes agonists and antagonists of NR6 expression. Antagonists of NR6 expression include antisense

35

molecules, ribozymes and co-suppression molecules. Agonists include molecules which increase promoter ability or interfere with negative regulatory mechanisms. Agonists of NR6 include molecules which overcome any negative regulatory mechanism. Antagonists of NR6 include antibodies and inhibitor peptide fragments.

Other derivatives contemplated by the present invention include a range of glycosylation variants from a completely unglycosylated molecule to a modified glycosylated molecule. Altered glycosylation patterns may result from expression of recombinant molecules in different host cells.

Another embodiment of the present invention contemplates a method for modulating expression of NR6 in a subject such as a human or mouse, said method comprising contacting the genetic sequence encoding NR6 with an effective amount of a modulator of NR6 expression for a time and under conditions sufficient to up-regulate or down-regulate or otherwise modulate expression of NR6. Modulating NR6 expression provides a means of modulating NR6-ligand interaction or NR6 stimulation of cell activities.

Another aspect of the present invention contemplates a method of modulating activity of NR6 in a human, said method comprising administering to said mammal a modulating effective amount of a molecule for a time and under conditions sufficient to increase or decrease NR6 activity. The molecule may be a proteinaceous molecule or a chemical entity and may also be a derivative of NR6 or its ligand or a chemical analogue or truncation mutant of NR6 or its ligand.

The present invention, therefore, contemplates a

pharmaceutical composition comprising NR6 or a derivative thereof or a modulator of NR6 expression or NR6 activity and one or more pharmaceutically acceptable carriers and/or diluents. These components are referred to as the Aactive ingredients@.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions (where water soluble) and sterile powders for the extemporaneous preparation of sterile injectable solutions. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dilution medium comprising, for example, water, ethanol, polyol (for example, glycerol, propylene glycol and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of surfactants. The preventions of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze-drying

technique which yield a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

5 When the active ingredients are suitably protected they may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsule, or it may be compressed into tablets, or it may be
10 incorporated directly with the food of the diet. For oral therapeutic administration, the active compound may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like.
15 Such compositions and preparations should contain at least 1% by weight of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 5 to about 80% of the weight of the unit. The amount of active
20 compound in such therapeutically useful compositions in such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 0.1 ug and 2000 mg of active
25 compound. Alternative dosage amounts include from about 1 Fg to about 1000 mg and from about 10 Fg to about 500 mg.

The tablets, troches, pills, capsules and the like may
30 also contain the components as listed hereafter: A binder such as gum, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as
35 magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavouring agent such as peppermint, oil of wintergreen,

or cherry flavouring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavouring such as cherry or orange flavour. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compound(s) may be incorporated into sustained-release preparations and formulations.

The present invention also extends to forms suitable for topical application such as creams, lotions and gels as well as a range of "paints" which are applied to skin and through which the active ingredients are absorbed.

Pharmaceutically acceptable carriers and/or diluents include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art and except insofar as any conventional media or agent is incompatible with the active ingredient, their use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units

suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the novel dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active material for the treatment of disease in living subjects having a diseased condition in which bodily health is impaired as herein disclosed in detail.

The principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as hereinbefore disclosed. A unit dosage form can, for example, contain the principal active compound in amounts ranging from 0.5 :g to about 2000 mg. Expressed in proportions, the active compound is generally present in from about 0.5 :g to about 2000 mg/ml of carrier. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients.

Dosages may also be expressed per body weight of the recipient. For example, from about 10 ng to about 1000 mg/kg body weight, from about 100 ng to about 500 mg/kg body weight and for about 1 Fg to above 250 mg/kg body weight may be administered.

The pharmaceutical composition may also comprise genetic molecules such as a vector capable of transfecting target cells where the vector carries a nucleic acid molecule capable of modulating NR6 expression or NR6

activity. The vector may, for example, be a viral vector.

5 Still another aspect of the present invention is directed to antibodies to NR6 and its derivatives. Such antibodies may be monoclonal or polyclonal and may be selected from naturally occurring antibodies to NR6 or may be specifically raised to NR6 or derivatives thereof. In the case of the latter, NR6 or its
10 derivatives may first need to be associated with a carrier molecule. The antibodies and/or recombinant NR6 or its derivatives of the present invention are particularly useful as therapeutic or diagnostic agents. For example, NR6 antibodies or antibodies to its ligand
15 may act as antagonists.

For example, NR6 and its derivatives can be used to screen for naturally occurring antibodies to NR6. These may occur, for example in some autoimmune diseases.
20 Alternatively, specific antibodies can be used to screen for NR6. Techniques for such assays are well known in the art and include, for example, sandwich assays and ELISA. Knowledge of NR6 levels may be important for diagnosis of certain cancers or a predisposition to
25 cancers or for monitoring certain therapeutic protocols.

Antibodies to NR6 of the present invention may be monoclonal or polyclonal. Alternatively, fragments of antibodies may be used such as Fab fragments.
30 Furthermore, the present invention extends to recombinant and synthetic antibodies and to antibody hybrids. A "synthetic antibody" is considered herein to include fragments and hybrids of antibodies. The antibodies of this aspect of the present invention are
35 particularly useful for immunotherapy and may also be used as a diagnostic tool for assessing apoptosis or monitoring the program of a therapeutic regimen.

For example, specific antibodies can be used to screen for NR6 proteins. The latter would be important, for example, as a means for screening for levels of NR6 in a cell extract or other biological fluid or purifying NR6
5 made by recombinant means from culture supernatant fluid. Techniques for the assays contemplated herein are known in the art and include, for example, sandwich assays and ELISA.

10 It is within the scope of this invention to include any second antibodies (monoclonal, polyclonal or fragments of antibodies or synthetic antibodies) directed to the first mentioned antibodies discussed above. Both the first and second antibodies may be used in detection
15 assays or a first antibody may be used with a commercially available anti-immunoglobulin antibody. An antibody as contemplated herein includes any antibody specific to any region of NR6.

20 Both polyclonal and monoclonal antibodies are obtainable by immunization with the enzyme or protein and either type is utilizable for immunoassays. The methods of obtaining both types of sera are well known in the art. Polyclonal sera are less preferred but are relatively
25 easily prepared by injection of a suitable laboratory animal with an effective amount of NR6, or antigenic parts thereof, collecting serum from the animal, and isolating specific sera by any of the known immunoadsorbent techniques. Although antibodies
30 produced by this method are utilizable in virtually any type of immunoassay, they are generally less favoured because of the potential heterogeneity of the product.

The use of monoclonal antibodies in an immunoassay is
35 particularly preferred because of the ability to produce them in large quantities and the homogeneity of the product. The preparation of hybridoma cell lines for

monoclonal antibody production derived by fusing an
immortal cell line and lymphocytes sensitized against
the immunogenic preparation can be done by techniques
which are well known to those who are skilled in the
5 art.

Another aspect of the present invention contemplates a
method for detecting NR6 in a biological sample from a
subject said method comprising contacting said
10 biological sample with an antibody specific for NR6 or
its derivatives or homologues for a time and under
conditions sufficient for an antibody-NR6 complex to
form, and then detecting said complex.

The presence of NR6 may be accomplished in a number of
15 ways such as by Western blotting and ELISA procedures.
A wide range of immunoassay techniques are available as
can be seen by reference to US Patent Nos. 4,016,043, 4,
424,279 and 4,018,653. These, of course, includes both
single-site and two-site or "sandwich" assays of the
20 non-competitive types, as well as in the traditional
competitive binding assays. These assays also include
direct binding of a labelled antibody to a target.

Sandwich assays are among the most useful and commonly
25 used assays and are favoured for use in the present
invention. A number of variations of the sandwich assay
technique exist, and all are intended to be encompassed
by the present invention. Briefly, in a typical forward
assay, an unlabelled antibody is immobilized on a solid
30 substrate and the sample to be tested brought into
contact with the bound molecule. After a suitable
period of incubation, for a period of time sufficient to
allow formation of an antibody-antigen complex, a second
antibody specific to the antigen, labelled with a
35 reporter molecule capable of producing a detectable
signal is then added and incubated, allowing time
sufficient for the formation of another complex of

antibody-antigen-labelled antibody. Any unreacted material is washed away, and the presence of the antigen is determined by observation of a signal produced by the reporter molecule. The results may either be

5 qualitative, by simple observation of the visible signal, or may be quantitated by comparing with a control sample containing known amounts of hapten. Variations on the forward assay include a simultaneous assay, in which both sample and labelled antibody are

10 added simultaneously to the bound antibody. These techniques are well known to those skilled in the art, including any minor variations as will be readily apparent. In accordance with the present invention, the sample is one which might contain NR6 including cell

15 extract, tissue biopsy or possibly serum, saliva, mucosal secretions, lymph, tissue fluid and respiratory fluid. The sample is, therefore, generally a biological sample comprising biological fluid but also extends to fermentation fluid and supernatant fluid such as from a

20 cell culture.

In the typical forward sandwich assay, a first antibody having specificity for the NR6 or antigenic parts thereof, is either covalently or passively bound to a

25 solid surface. The solid surface is typically glass or a polymer, the most commonly used polymers being cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene. The solid supports may be in the form of tubes, beads, discs of microplates, or any

30 other surface suitable for conducting an immunoassay. The binding processes are well-known in the art and generally consist of cross-linking covalently binding or physically adsorbing, the polymer-antibody complex is washed in preparation for the test sample. An aliquot

35 of the sample to be tested is then added to the solid phase complex and incubated for a period of time sufficient (e.g. 2-40 minutes or overnight if more

convenient) and under suitable conditions (e.g. from about room temperature to about 37°C) to allow binding of any subunit present in the antibody. Following the incubation period, the antibody subunit solid phase is washed and dried and incubated with a second antibody specific for a portion of the hapten. The second antibody is linked to a reporter molecule which is used to indicate the binding of the second antibody to the hapten.

10

An alternative method involves immobilizing the target molecules in the biological sample and then exposing the immobilized target to specific antibody which may or may not be labelled with a reporter molecule. Depending on the amount of target and the strength of the reporter molecule signal, a bound target may be detectable by direct labelling with the antibody. Alternatively, a second labelled antibody, specific to the first antibody is exposed to the target-first antibody complex to form a target-first antibody-second antibody tertiary complex. The complex is detected by the signal emitted by the reporter molecule.

In another alternative method, the NR6 ligand is immobilised to a solid support and a biological sample containing NR6 brought into contact with its immobilised ligand. Binding between NR5 and its ligand can then be determined using an antibody to NR6 which itself may be labelled with a reporter molecule or a further anti-immunoglobulin antibody labelled with a reporter molecule could be used to detect antibody bound to NR6.

By "reporter molecule" as used in the present specification, is meant a molecule which, by its chemical nature, provides an analytically identifiable signal which allows the detection of antigen-bound antibody. Detection may be either qualitative or

quantitative. The most commonly used reporter molecules in this type of assay are either enzymes, fluorophores or radionuclide containing molecules (i.e. radioisotopes) and chemiluminescent molecules.

5 In the case of an enzyme immunoassay, an enzyme is conjugated to the second antibody, generally by means of glutaraldehyde or periodate. As will be readily recognized, however, a wide variety of different conjugation techniques exist, which are readily
10 available to the skilled artisan. Commonly used enzymes include horseradish peroxidase, glucose oxidase, beta-galactosidase and alkaline phosphatase, amongst others. The substrates to be used with the specific enzymes are generally chosen for the production, upon hydrolysis by
15 the corresponding enzyme, of a detectable colour change. Examples of suitable enzymes include alkaline phosphatase and peroxidase. It is also possible to employ fluorogenic substrates, which yield a fluorescent product rather than the chromogenic substrates noted
20 above. In all cases, the enzyme-labelled antibody is added to the first antibody hapten complex, allowed to bind, and then the excess reagent is washed away. A solution containing the appropriate substrate is then added to the complex of antibody-antigen-antibody. The
25 substrate will react with the enzyme linked to the second antibody, giving a qualitative visual signal, which may be further quantitated, usually spectrophotometrically, to give an indication of the amount of hapten which was present in the sample.
30 "Reporter molecule" also extends to use of cell agglutination or inhibition of agglutination such as red blood cells on latex beads, and the like.

35 Alternately, fluorescent compounds, such as fluorescein and rhodamine, may be chemically coupled to antibodies without altering their binding capacity. When activated by illumination with light of a particular wavelength,

the fluorochrome-labelled antibody adsorbs the light energy, inducing a state to excitability in the molecule, followed by emission of the light at a characteristic colour visually detectable with a light microscope. As in the EIA, the fluorescent labelled antibody is allowed to bind to the first antibody-hapten complex. After washing off the unbound reagent, the remaining tertiary complex is then exposed to the light of the appropriate wavelength the fluorescence observed indicates the presence of the hapten of interest. Immunofluorescence and EIA techniques are both very well established in the art and are particularly preferred for the present method. However, other reporter molecules, such as radioisotope, chemiluminescent or bioluminescent molecules, may also be employed.

The present invention also contemplates genetic assays such as involving PCR analysis to detect the NR6 gene or its derivatives. Alternative methods or methods used in conjunction include direct nucleotide sequencing or mutation scanning such as single stranded conformational polymorphisms analysis (SSCP) as specific oligonucleotide hybridisation, as methods such as direct protein truncation tests.

The nucleic acid molecules of the present invention may be DNA or RNA. When the nucleic acid molecule is in a DNA form, it may be genomic DNA or cDNA. RNA forms of the nucleic acid molecules of the present invention are generally mRNA.

Although the nucleic acid molecules of the present invention are generally in isolated form, they may be integrated into or ligated to or otherwise fused or associated with other genetic molecules such as vector molecules and in particular expression vector molecules. Vectors and expression vectors are generally capable of

replication and, if applicable, expression in one or both of a prokaryotic cell or a eukaryotic cell. Preferably, prokaryotic cells include *E. coli*, *Bacillus sp* and *Pseudomonas sp*. Preferred eukaryotic cells
5 include yeast, fungal, mammalian and insect cells.

Accordingly, another aspect of the present invention contemplates a genetic construct comprising a vector portion and a mammalian and more particularly a human
10 NR6 gene portion, which NR6 gene portion is capable of encoding an NR6 polypeptide or a functional or immunologically interactive derivative thereof.

Preferably, the NR6 gene portion of the genetic
15 construct is operably linked to a promoter on the vector such that said promoter is capable of directing expression of said NR6 gene portion in an appropriate cell.

20 In addition, the NR6 gene portion of the genetic construct may comprise all or part of the gene fused to another genetic sequence such as a nucleotide sequence encoding maltose binding protein or glutathione-S-transferase or part thereof.

25 The present invention extends to such genetic constructs and to prokaryotic or eukaryotic cells comprising same.

The present invention also extends to any or all
30 derivatives of NR6 including mutants, part, fragments, portions, homologues and analogues or their encoding genetic sequence including single or multiple nucleotide or amino acid substitutions, additions and/or deletions to the naturally occurring nucleotide or amino acid
35 sequence.

NR6 may be important for the proliferation,

differentiation and survival of a diverse array of cell types. Accordingly, it is proposed that NR6 or its functional derivatives be used to regulate development, maintenance or regeneration in an array of different cells and tissues *in vitro* and *in vivo*. For example, NR6 is contemplated to be useful in modulating neuronal proliferation, differentiation and survival.

Soluble NR6 polypeptides are also contemplated to be useful in the treatment of a range of diseases, injuries or abnormalities.

Membrane bound or soluble NR6 may be used *in vitro* on nerve cells or tissues to modulate proliferation, differentiation or survival, for example, in grafting procedures or transplantation.

As stated above, the NR6 of the present invention or its functional derivatives may be provided in a pharmaceutical composition comprising the NR6 together with one or more pharmaceutically acceptable carriers and/or diluents. In addition, the present invention contemplates a method of treatment comprising the administration of an effective amount of a NR6 of the present invention. The present invention also extends to antagonists and agonists of NR6s and their use in therapeutic compositions and methodologies.

A further aspect of the present invention contemplates the use of NR6 or its functional derivatives in the manufacture of a medicament for the treatment of NR6 mediated conditions defective or deficient.

Still a further aspect of the present invention contemplates a ligand for NR6 preferably, in isolated or recombinant form or a derivative of said ligand.

The present invention further contemplates knockout animals such as mice or other murine species for the NR6 gene including homozygous and heterozygous knockout animals. Such animals provide a particularly useful
5 live in vivo model for studying the effects of NR6 as well as screening for agents capable of acting as agonists or antagonists of NR6.

According to this embodiment there is provided a
10 transgenic animal comprising a mutation in at least one allele of the gene encoding NR6. Additionally, the present invention provides a transgenic animal comprising a mutation in two alleles of the gene encoding NR6. Preferably, the transgenic animal is a
15 murine animal such as a mouse or rat.

The present invention is further described by the following non-limiting Figures and Examples.

20 In the Figures:

Figure 1 is a diagrammatic representation showing expansion of sequenced region of the mouse NR6 gene indicating splicing patterns seen in the three forms of
25 NR6 cDNA, NR6.1, NR6.2 and NR6.3.

Figure 2 is a representation of the nucleotide sequence of the mouse NR6 gene, containing exons encoding the cDNA from nucleotide 148 encoding D50 of the cDNAs shown
30 in SEQ ID NOs:12 and 14 to the end of the 3N untranslated region shared by both NR6.1, NR6.2 and NR6.3. In this figure, this region encompasses nucleotides g1182 to g6617. This sequence is also defined in SEQ ID NO:28.

35

Figure 3 is a representation of the nucleotide sequence of the mouse genomic NR6 gene with additional 5N

sequences. The coding exons of NR6 span approximately 11kb of the mouse genome. There are 9 coding exons separated by 8 introns:

	exon1	at least 239nt	intron1	5195nt
5	exon 2	282nt	intron2	214nt
	exon3	130nt	intron3	107nt
	exon4	170nt	intron4	1372nt
	exon5	158nt	intron5	68nt
	exon6	169nt	intron6	2020nt
10	exon6	188nt	intron7	104nt
	exon8	43nt	intron8	181nt
	exon9	252nt		

Exon 1 encoding the signal sequence, exon 2 the Ig-like domain, exons 3 to 6 the hemopoietin domain. Exons 7, 8 and 9 are alternatively spliced.

Figure 4 is a diagrammatic representation showing the genomic structure of murine NR-6.

Figure 5 is a diagrammatic representation showing targetting of the NR6 locus by homologous recombination.

Single and three letter abbreviations for amino acid residues used in the specification are summarised in Table 2:

5

TABLE 2

	Amino Acid	Three-letter Abbreviation	One-letter Symbol
10	Alanine	Ala	A
	Arginine	Arg	R
	Asparagine	Asn	N
	Aspartic acid	Asp	D
	Cysteine	Cys	C
15	Glutamine	Gln	Q
	Glutamic acid	Glu	E
	Glycine	Gly	G
	Histidine	His	H
	Isoleucine	Ile	I
20	Leucine	Leu	L
	Lysine	Lys	K
	Methionine	Met	M
	Phenylalanine	Phe	F
	Proline	Pro	P
25	Serine	Ser	S
	Threonine	Thr	T
	Tryptophan	Trp	W
	Tyrosine	Tyr	Y
	Valine	Val	V
30	Any residue	Xaa	X

TABLE 3
SUMMARY OF SEQ ID NO.

	Sequence	SEQ ID NO.
5	Amino acid sequence WSXWS	1
	Oligonucleotide primers and probes listed in Example 1	2-11
	Nucleotide sequence of NR6.1 ¹	12
	Amino acid sequence of NR6.1	13
10	Nucleotide sequence of NR6.2 ²	14
	Amino acid sequence of NR6.2	15
	Nucleotide sequence of NR6.3 ³	16
	Amino acid sequence of NR6.3	17
15	Nucleotide sequence of products generated by 5N RACE of brain cDNA using NR6 specific primers ⁴	18
	Amino acid sequence of SEQ ID NO:18	19
	Nucleotide sequence unique to 5N RACE of brain cDNA	20
20	Amino acid sequence for SEQ ID NO:20	21
	Unspliced murine NR6 nucleotide sequence	22
	PCR product for human NR6	23
	Nucleotide sequence of clone HFK-66 encoding human NR6	24
25	Amino acid sequence of SEQ ID NO:24	25
	Oligonucleotide sequences UP1 and LP1, respectively	26-27
	Genomic nucleotide sequence of murine NR6	28
	Amino acid sequence of SEQ ID NO:28	29
30	Murine NR6.1 oligonucleotide primers	30, 31
	Murine IL-3 signal sequence	32
	Linker sequence for mouse IL-3 signal sequence and FLAG epitope	33-35
35	Genomic nucleotide sequence of murine NR6 containing additonal 5N sequence	38
	Oligonucleotide 2199 and 2200, respectively	36, 37
	N-terminal region of NR6	39

¹The polyadenylation signal AATAAATAAA is at nucleotide position 1451 to 1460; NR6.1 (SEQ ID NO:12) and NR6.2 (SEQ ID NO:14) are identical to nucleotide 1223 encoding Q407, the represents the end of an exon. NR6.1 splices out an exon present only in NR6.2 and uses a different reading frame for the final exon which is shared with NR6.2; this corresponds to amino acids VLPACL at amino acid residue positions 408-413. The region of 3N-untranslated DNA shared by NR6.1, NR6.2 and NR6.3 is from nucleotide 1240 to 1475. The WSXWS motif is at amino acid residues 330 to 334.

²The polyadenylation signal AATAAA is at nucleotide positions 1494 to 1503. The WSXWS motif is at amino acid residues 330 to 334. NR6.1 and NR6.2 are identical to nucleotide 1223 encoding Q407 which represents the end of an exon. NR6.2 splices in an exon beginning at amino acid residue D408, nucleotide 1224 and ends at residue G422, nucleotide 1264. The region of 3N-untranslated DNA shared by NR6.1, NR6.2 and NR6.3 is from nucleotide position 1283 to 1517.

³The nucleotide and amino acid numbering corresponds to SEQ ID NO:12 and 14. The WSXWS motif is at amino acid residues 330 to 334. The polyadenylation signal AATAAATAAA is from nucleotide 1781 to 1780. NR6.1, NR6.2 and NR6.3 are identical to nucleotide 1223 encoding Q407, this represents the end of an exon. NR6.3 fails to splice from this position and, therefore, translation continues through the intron, giving rise to the C-terminal protein region from amino acid residues 408 to 461. The region of 3N untranslated DNA shared by NR6.1, NR6.2 and NR6.3 is from nucleotide 1469 to 1804.

⁴The nucleotide sequence is identical to NR6.1, NR6.2 and NR6.3 from nucleotide C151, the first nucleotide for Pro51. The numbering from this nucleotide is the same

as for SEQ ID NO:14 and 16. The 5N of this point is unique to the products generated by 5N RACE not being found in NR6.1, NR6.2 and NR6.3 and is represented in SEQ ID NOs:20 and 21.

5

⁵Structure of the murine genomic NR6 locus. The coding exons of NR6 span approximately 11kb of the mouse genome. There are 9 coding exons separated by 8 introns:

10

exon 1 at least 239nt	intron1 5195nt
exon 2 282nt	intron2 214nt
exon 3 130nt	intron3 107nt
exon 4 170nt	intron 4 1372nt
exon 5 158nt	intron5 68nt
exon 6 169nt	intron6 2020nt
exon 7 188nt	intron7 104nt
exon 8 43nt	intron8 181nt
exon 9 252nt	

20

Exon 1 encodes the signal sequence, exon 2 the Ig-like domain, exons 3 to 6 the hemopoietin domain. Exons 7, 8 and 9 are alternatively spliced.

25 The NRG molecules of the present invention have a range of utilities referred to in the subject specification. Additional utilities include:

1. Identification of molecules that interact with NR6.

30 These may include :

a) a corresponding ligand using standard orphan receptor techniques (26),

35 b) monoclonal antibodies that act either as receptors antagonists or agonists,

c) mimetic or antagonistic peptides isolated using phage display technology (27,28),

5 d) small molecule natural products that act either as antagonists or agonists.

2. Development of diagnostics to detect deletions/rearrangements in the NR6 gene.

10 The NR6 knock-out mice studies described herein provide a useful model for this utility. There are also applications in the field of reproduction. For example, people can be tested for their NR6 status. NR6 +/- carriers might be expected to give rise to offspring with developmental problems.

EXAMPLE 1
Oligonucleotides

M116: 5' ACTCGCTCCAGATTCCCGCCTTTT 3' [SEQ ID NO:2]
 5 M108: 5' TCCCGCCTTTTTCGACCCATAGAT 3' [SEQ ID NO:3]
 M159: 5' GGTACTTGGCTTGAAGAGGAAAT 3' [SEQ ID NO:4]
 M242: 5' CGGCTCACGTGCACGTCGGGTGGG 3' [SEQ ID NO:5]
 M112: 5' AGCTGCTGTAAAGGGCTTCTC 3' [SEQ ID NO:6]
 WSDWS 5' (A/G)CTCCA(A/G)TC(A/G)CTCCA 3' [SEQ ID NO:7]
 10 WSEWS 5' (A/G)CTCCA(C/T)TC(A/G)CTCCA 3' [SEQ ID NO:8]
 1944 5' AAGTGTGACCATCATGTGGAC 3' [SEQ ID NO:9]
 2106 5' GGAGGTGTTAAGGAGGCG 3' [SEQ ID NO:10]
 2120 5' ATGCCCCGCGGGTCGCCCCG 3' [SEQ ID NO:11]

15

EXAMPLE 2

Isolation of initial NR6 cDNA clones using oligonucleotides designed against the conserved WSXWS motif found in members of the haemopoietin receptor family

20

(i) A commercial adult mouse testis cDNA library cloned into the UNI-ZAP bacteriophage (Stratagene, CA, USA; Catalogue numbers 937 308) was used to infect *Escherichia coli* of the strain LE392. Infected bacteria
 25 were grown on twenty 150 mm agar plates, to give approximately 50,000 plaques per plate. Plaques were then transferred to duplicate 150 mm diameter nylon membranes (Colony/Plaque Screen, NEN Research Products, MA, USA), bacteria were lysed and the DNA was denatured
 30 and fixed by autoclaving at 100°C for 1 min with dry exhaust. The filters were rinsed twice in 0.1%(w/v) sodium dodecyl sulfate (SDS), 0.1 x SSC (SSC is 150 mM sodium chloride, 15 mM sodium citrate dihydrate) at room temperature and pre-hybridized overnight at 42°C in 6 x
 35 SSC containing 2 mg/ml bovine serum albumin, 2 mg/ml Ficoll, 2 mg/ml polyvinylpyrrolidone, 100 mM ATP, 10 mg/ml tRNA, 2 mM sodium pyrophosphate, 2 mg/ml salmon

sperm DNA, 0.1% (w/v) SDS and 200 mg/ml sodium azide. The pre-hybridisation buffer was removed. 1.2 Fg of the degenerate oligonucleotides for hybridization (WSDWS; Example 1) were phosphorylated with T4 polynucleotide kinase using 960 mCi of $\gamma^{32}\text{P}$ -ATP (Bresatec, S.A., Australia). Unincorporated ATP was separated from the labelled oligonucleotide using a pre-packed gel filtration column (NAP-5; Pharmacia, Uppsala, Sweden). Filters were hybridized overnight at 42°C in 80 ml of the prehybridisation buffer containing 0.1% (w/v) SDS, rather than NP40, and $10^6 - 10^7$ cpm/ml of labelled oligonucleotide. Filters were briefly rinsed twice at room temperature in 6 x SSC, 0.1% (v/v) SDS, twice for 30 min at 45°C in a shaking waterbath containing 1.5 l of the same buffer and then briefly in 6 x SSC at room temperature. Filters were then blotted dry and exposed to autoradiographic film at -70°C using intensifying screens, for 7 - 14 days prior to development. Plaques that appeared positive on orientated duplicate filters were picked, eluted in 1 ml of 100 mM NaCl, 10 mM MgCl_2 , 10 mM Tris.HCl pH7.4 containing 0.5% (w/v) gelatin and 0.5% (v/v) chloroform and stored at 4°C. After 2 days LE392 cells were infected with the eluate from the primary plugs and replated for the secondary screen. This process was repeated until hybridizing plaques were pure.

Once purified, positive cDNAs were excised from the ZAP II bacteriophage according to the manufacturer's instructions (Stratagene, CA, USA) and cloned into the plasmid pBluescript. A CsCl purified preparation of the DNA was made and this was sequenced on both strands. Sequencing was performed using an Applied Biosystems automated DNA sequencer, with fluorescent dideoxynucleotide analogues according to the manufacturer's instructions. The DNA sequence was analysed using software supplied by Applied Biosystems.

Two clones isolated from the mouse testis cDNA library shared large regions of nucleotide sequence identity 68-1 and 68-2 and appeared to encode a novel member of the haemopoietin receptor family and the inventors gave the putative receptor the working name "NR6".

(ii) In a parallel series of experiments, a commercial mouse brain cDNA library (STRATAGENE #967319, Balb/c day-20, whole brain cDNA/Uni-ZAP XR Vector) was used to infect *E.coli* strain XL1-Blue MRF=. Infected bacteria were grown on 90x135mm square agar plates to give about 25,000 plaques per plate. Plaques were then transferred to positively charged nylon membranes, Hybond-N(+) (Amersham RPN 203B), bacteria were lysed and the DNA was denatured with denaturing 0.5 M NaOH, 1.5 M NaCl at room temperature for 7 min. The membranes were neutralized with 0.5 M Tris-HCL pH7.2, 1.5 M NaCl, 1 mM EDTA at room temperature for 10 min before the DNA fixation by UV crosslinking.

A mixture of WSDWS and WSEWS oligonucleotide probes (SEQ ID NOs: 7 and 8) were labelled with a [γ - 32 P]-ATP (TOYOBO #PNK-104 Kination kit). The membranes from the mouse brain cDNA library were then hybridized with the mixture of WSDWS and WSEWS oligonucleotide probes in the Rapid Hybridization Buffer (Amersham, RPN1636) at 42°C for 16 hours. Filters were washed with 1xSSC/0.1% (w/v) SDS at 42°C before autoradiography. Plaques that appeared positive on orientated duplicate filters were picked and replated on *E. coli*, XL1-Blue MRFN with the process of immobilisation on nylon membranes, hybridization of membranes with oligonucleotide probes, washing and autoradiography repeated until pure plaques had been obtained.

The cDNA fragment from pure positively hybridizing plaques was isolated by excision with the helper phage

- strain ExAssist according to the manufacturer's instructions (Stratagene, #967319). Sequencing was performed after the amplification with Ampli-Taq DNA polymerase and Taq dideoxy terminator cycle sequencing kit (Perkin Elmer, #401150) by 25 cycles of 96°C for 10 sec, 50°C for 5 sec, 60°C for 4 min followed by 60°C for 5 min with the sequencing primers on an ABI model 377 DNA sequencer.
- 10 One clone, MBC-8, from the mouse brain library shared large regions of nucleotide sequence identity with both the 68-1 and 68-2 clones isolated from the mouse testis cDNA library.
- 15 (iii) In a third series of experiments, total RNA was prepared from the mouse osteoblastic cell line, KUSA, according to the method of Chirgwin et al. (15), and poly(A)+RNA was further purified by oligo(dT)-cellulose chromatography (Pharmacia Biotech). Complementary DNA
- 20 was synthesized by oligo(dT) priming, inserted into the UniZAP XR directional cloning vector (Stratagene), and packaged into 8 phage using Gigapack Gold (Stratagene), yielding 1.25×10^7 independent clones.
- 25 Approximately 10^6 clones were screened essentially as described in (ii) above. Briefly, probes were labeled with ^{32}P using T4 polynucleotide kinase and prehybridization was performed for 4 hr in the Rapid hybridization buffer (Amersham LIFE SCIENCE) at 42°C.
- 30 Filters (Hybond N+, Amersham) were then hybridized for 19 hr under the same condition with the addition of ^{32}P -labeled WSXWS mix oligonucleotides and washed 3 times. The final wash was for 30 min in 1 x SSPE, 0.1% (w/v) SDS at 42°C. Filters were then exposed with an
- 35 intensifying screen to Kodak X-OMAT AR film for 5 days.
- Isolated clones were subjected to the *in vivo* excision

of pBluescript SK(-) phagemid (Stratagene), and plasmid DNA was prepared by the standard method. DNA sequences were determined using an ABI PRISM 377 DNA Sequencer (Perkin Elmer) with appropriate synthetic
5 oligonucleotide primers. A clone pKUSA166 shared large regions of nucleotide sequence identity with the MBC-8, 68-1 and 68-2 clones isolated from the mouse brain and testis cDNA libraries.

EXAMPLE 3

10 Isolation of further NR6 cDNA clones using probes specific for NR6

(i) In order to identify other cDNA libraries containing cDNA clones for NR6, the inventors performed
15 PCR upon 1 μ l aliquots of λ -bacteriophage cDNA libraries made from mRNA from various human tissues and using oligonucleotides 2070 and 2057, designed from the sequence of 68-1 and 68-2, as primers. Reactions
20 contained 5 μ l of 10 x concentrated PCR buffer (Boehringer Mannheim GmbH, Mannheim, Germany), 1 μ l of 10 mM dATP, dCTP, dGTP and dTTP, 2.5 μ l of the oligonucleotides HYB2 and either T3 or T7 at a concentration of 100 mg/ml, 0.5 μ l of Taq polymerase
25 (Boehringer Mannheim GmbH) and water to a final volume of 50 μ l. PCR was carried out in a Perkin-Elmer 9600 by heating the reactions to 96°C for 2 min and then for 25 cycles at 96°C for 30 sec, 55°C for 30 sec and 72°C for 2 min. PCR products were resolved on an agarose gel,
30 immobilized on a nylon membrane and hybridized with ³²P-labelled oligonucleotide 1943 (SEQ ID NO:42).

In addition to the original library, a mouse brain cDNA library appeared to contain NR6 cDNAs. These were
35 screened using a ³²P-labelled oligonucleotides 1944, 2106, 2120 (Example 1) or with a fragment of the original NR6 cDNA clone from 68-1 (nucleotide 934 to the

end of NR6.1 in Figure 1) labelled with ^{32}P using a random decanucleotide labelling kit (Bresatec). Conditions used were similar to those described in (i) above except that for the labelled oligonucleotides, filters were washed at 55°C rather than 45°C , while for the NR6 cDNA fragment prehybridization and hybridization was carried out in 2xSSC and filters were washed at 0.2 x SSC at 65°C . Again, as described in (i) above, positively hybridising plaques were purified, the cDNAs were recovered and cloned into plasmids pBluescript II or pUC19. Independent cDNA clones were sequenced on both strands.

Using this procedure, 6 further clones, 68-5, 68-35, 68-41, 68-51, 68-77 and 73-23, contained large regions of sequence identity with 68-1, 68-2, MBC-8 and pKUSA166.

In a parallel series of experiments, further screening was performed with hybridization probes prepared from the 1.7 kbp EcoRI-XhoI fragment excised from pKUSA166. This fragment was excised and labeled with ^{32}P by using T7QuickPrime Kit (Pharmacia Biotech). Approximately 6×10^5 clones were screened. Hybond N+ filters (Amersham) were first prehybridized for 4hr at 42°C in 50% (v/v) formamide, 5xSSPE, 5xDenhardt's solution, 0.1% (w/v) SDS, and 0.1mg/ml denatured salmon sperm DNA. Hybridization was for 16 hours under the same conditions with the addition of ^{32}P -labelled NR6- cDNA fragment probes. Finally the filters were washed once for 1hr in 0.2xSSC, 0.1% (w/v) SDS at 68°C . Eight clones were isolated, and phage clones were subjected to the *in vivo* excision of the pBluescript SK(-) phagemid (Stratagene). The plasmid DNAs were prepared by the standard method. DNA sequences were determined by an ABI PRISM 377 DNA Sequencer using appropriate synthetic oligonucleotide primers.

Using this procedure 8 further clones from the KUSA library contained large regions of sequence identity with 68-1, 68-2, MBC-8, pKUSA166, 68-5, 68-35, 68-41, 68-51, 68-77 and 73-23 were isolated.

5

EXAMPLE 4**Isolation of genomic DNA encoding NR6**

DNA encoding the murine NR6 genomic locus was also isolated using the 68-1 cDNA as a probe. Two positive clones, 2-2 and 57-3, were isolated from a mouse 129/Sv strain genomic DNA library cloned into λ FIX. These clones were overlapping and the position of the restriction sites, introns and exons were determined in the conventional manner. The region of the genomic clones containing exons and the intervening introns were sequenced on both strands using an Applied Biosystems automated DNA sequencer, with fluorescent dideoxynucleotide analogues according to the manufacturer's instructions. Figure 2 shows the nucleotide sequence and corresponding amino acid sequence of the translation regions. This is also shown in SEQ ID NOs:30 and 31. Figure 3 provides the genomic NR6 gene sequence but with additional 5N sequence. This is also represented in SEQ ID NO:38 in relation to this sequence. The coding exons of NR6 span approximately 11kb of the mouse genome. There are 9 coding exons separated by 8 introns:

30	exon1	at least 239nt	intron1	5195nt
	exon2	282nt	intron2	214nt
	exon3	130nt	intron3	107nt
	exon4	170nt	intron4	1372nt
	exon5	158nt	intron5	68nt
35	exon6	169nt	intron6	2020nt
	exon7	188nt	intron7	104nt
	exon8	43nt	intron8	181nt

exon9 252nt

Exon 1 encodes the signal sequence, exon 2 the Ig-like domain, exons 3 to 6 the hemopoietin domain. Exons 7, 8 and 9 are alternatively spliced.

EXAMPLE 5

5N RACE analysis of NR6

5'-RACE was used to investigate the nature of the sequence 5' of nucleotide 960, encoding Ile321 of NR6.1, 2 and 3. The nucleotide and corresponding amino acid sequences are shown in SEQ ID NOs:12, 14 and 16, respectively. 5'-RACE was performed using Advantage KlenTaq polymerase (CLONTECH, CAT NO. K1905-1) on mouse brain Marathon-ready cDNA (CLONTECH, CAT NO. 7450-1) according to the manufacturer's instructions. Briefly, the first rounds of amplification were performed using 5µl of cDNA in a total volume of 50µl, with 1mM each of the primers AP1&M116 [SEQ ID NO:2] or AP1&M159 [SEQ ID NO:4] by 35 cycles of 94°C x 0.5min, 68°C x 2.0min on GeneAmp 2400 (Perkin-Elmer). An amount of 5µl of 50-fold diluted product from the first amplification was then re-amplified; for the products generated with primers AP1 and M116 [SEQ ID NO:2] in the first amplification, 1 mM of the primers AP2&M108 [SEQ ID NO:3] were used in the second amplification. For the products generated with primers AP1 and M116 [SEQ ID NO:2] in the first amplification, two separate secondary reactions were performed, one reaction with 1 mM primers AP2&M242 [SEQ ID NO:5] and the other with 1 mM primers AP2&M112 [SEQ ID NO:6]. Amplification was achieved using 25 cycles of 94°C x 0.5min, 68°C x 2.0min. These samples were analyzed by agarose gel electrophoresis. When a single ethidium bromide staining amplification

product was observed, it was purified by QIAquick PCR purification kit according to the manufacturer's instructions (QIAGEN, CAT NO. DG-0281) and its sequence was directly determined using both primers used in the secondary amplification step, that is AP2 and either M108 [SEQ ID NO:3], M242 [SEQ ID NO:5] or M112 [SEQ ID NO:6].

EXAMPLE 6

Cloning of NR6

From the initial screens of mouse brain and testis cDNA libraries with the degenerate WSXWS oligonucleotides and subsequent screening of cDNA libraries from mouse testis, mouse brain and the KUSA osteoblastic cells line a total of 18 NR6 cDNAs have been isolated. Nucleotide sequence of NR6 was also determined from 5'RACE analysis of brain cDNA. Additionally, two murine genomic DNA clones encoding NR6 have also been isolated.

Comparison of the NR6 cDNA clones revealed a common region of nucleotide sequence which included a 123 base pairs 5'-untranslated region and 1221 base pairs open reading frame, stretching from the putative initiation methionine, Met1 to Gln407 (SEQ ID NOS:12, 14 and 16, respectively). Within this common open reading frame, a haemopoietin receptor domain was observed which contained the four conserved cysteine residues and the five amino acid motif WSXWS typical of members of the haemopoietin receptor family, was observed.

Further analyses revealed that after nucleotide 1221, three different classes of NR6 cDNAs could be found, these were termed NR6.1, NR6.2 and NR6.3 (SEQ ID NOS:12, 14 and 16, respectively). Each encoded a receptor that appeared to lack a classical transmembrane domain and, would, therefore be likely to be secreted into the

extracellular environment. Although the putative C-terminal region of the three classes of NR6 proteins appear to be different, the cDNAs encoding them also had a common region of 3'-untranslated region.

5

With regard to SEQ ID NOs:12, 14 and 16, the number of both nucleotides and amino acids begins at the putative initiation methionine. NR6.1 and NR6.2 are identical to nucleotide 1223 encoding Q407, this represents the end of an exon. NR6.1 splices out an exon present only in NR6.2 and uses a different reading frame for the final exon which is shared with NR6.2. The 3N-untranslated region is shared by NR6.1, NR6.2 and NR6.3, NR6.2 splices in an exon starting with nucleotide 1224 encoding D408 and ending with nucleotide 1264 encoding the first nucleotide in the codon for G422 and uses a different reading frame for the final exon which is shared with NR6.2 (see Figure 1). NR6.3 fails to splice from position nucleotide 1224, therefore, translation continues through the intron, giving rise to the C-terminal protein region.

The sequence of NR6 cDNA products generated by 5'-RACE amplification from mouse brain cDNA preparation is shown in SEQ ID NO:18. The nucleotide sequence identified using 5'-RACE appeared to be identical to the sequence of cDNAs encoding NR6.1, NR6.2, and NR6.3 from nucleotide C151, the first nucleotide for the codon for Pro51. 5' of this nucleotide, the sequences diverged and the sequence is unique not being found in NR6.1, NR6.2 or NR6.3. Additionally, there is a single nucleotide difference, with the sequence from the RACE containing an G rather than an A at nucleotide 475, resulting in Thr159 becoming Ala.

35

Analysis of the genomic clones, revealed that they were overlapping and contained exons encoding the majority of

the coding region of the three forms of NR6 (Figures 1, 2 and 3). These genomic clones, contained exons encoding from Asp50 (nucleotide 148) of the NR6 cDNAs. Sequence 5' of this in the cDNAs, including the 5'-
5 untranslated region and the region encoding Met1 to Gln49 (SEQ ID NOs:12, 14 and 16), and the 5' end predicted from analysis of 5' RACE products (SEQ ID NO:18) were not present in the two genomic clones isolated.

10

Analysis of the NR6 genomic DNA clones also provided an explanation of the three classes of NR6 cDNAs found. It is likely that NR6.1, NR6.2 and NR6.3 arise through alternative splicing of NR6 mRNA (Figure 1). The last
15 amino acid residue that these different NR6 proteins are predicted to share is Gln407. SEQ ID NO:18 shows that Gln407 is the last amino acid encoded by the exon that covers nucleotides g5850 to g6037 (see Figure 2).

Alternative splicing from the end of this exon (Figure
20 1) accounts for the generation of cDNAs encoding NR6.1 (SEQ ID NO:12), NR6.2 (SEQ ID NO:14) and NR6.3 (SEQ ID NO:16). In the case of NR6.1, the region from g6038 to g6425 is spliced out, leading to juxtaposition of g6037 and g6426. In the case of NR6.2, the region from g6038
25 to 6141 is spliced out, an exon from 6142 to g6183 is retained and then this is followed by splicing out of the region from g6183 to g6425. NR6.3 appears to arise when there is no splicing from nucleotide g6038. For
30 all three forms, a secreted rather than transmembrane form is generated, these differ however in their predicted C-terminal region. The genomic NR6 sequence with additional 5N sequence is shown in Figure 3.

EXAMPLE 7

35

ESTs

Databases were searched with the murine NR6

corresponding to the unspliced version shown in SEQ ID NO:16. The murine NR6 sequence used is shown in SEQ ID NO:22.

The databases searched were:

5

(i) dbEST - Database of Expressed Sequence Tags
National Center for Biotechnology Information National
Library of Medicine, 38A, 8N8058600 Rockville Pike,
Bethesda, MD 20894 Phone: 0011-1-301-496-2475 Fax:
10 0015-1-301-480-9241 USA.

(ii) DNA Data Bank of Japan DNA Database Release 3689.
Prepared by: Sanzo Miyazawa Manager/Database
Administrator Hidenori Hayashida Scientific Reviewer
15 Yukiko Yamazaki/Eriko Hatada/Hiroaki Serizawa
Annotators/reviewers Motono Horie/Shigeko Suzuki/Yumiko
Satao Secretaries/typists DNA Data Bank of Japan National
Institute of Genetics Center for Genetic Information
research Laboratory of Genetic Information Analyses 1111
20 Yata Mishima, Shizuoka 411 Japan.

(iii) EMBL Nucleic Acid Sequence Data Bank Release
47.0.

25 (iv) EMBL Nucleic Acid Sequence Data Bank Weekly Updates
Since Release 44.

(v) Genetic Sequence Data Bank NCBI-GenBank Release 94
National Center for Biotechnology Information National
30 Library of Medicine, 38A, 8N805 8600 Rockville Pike,
Bethesda, MD 20894 Phone: 0011-1-301-495-2475 Fax:
0015-1-301-480-9241 USA.

(vi) Cumulative Updates since NCBI-GenBank Release 88
35 National Center for Biotechnology Information National
Library of Medicine, 38A, 8N805 8600 Rockville Pike,
Bethesda, MD 20894 USA.

The search of the databases with the murine probe identified several EST's having sequence similarity to the probe. The EST's were:

- 5 W66776 (murine sequence)
- MM5839 (murine sequence)
- AA014965 (murine sequence)
- W46604 (human sequence)
- W46603 (human sequence)
- 10 H14009 (human sequence)
- N78873 (human sequence)
- R87407 (human sequence).

EXAMPLE 8

15 Isolation of 3N cDNA clones encoding human NR6

PCR products encoding human NR6 were generated using oligonucleotides UP1 and LP1 (see below) based on human ESTs (Genbank Acc:H14009, Genbank Acc:AA042914) that
20 were identified from databases searched with murine NR6 sequence (SEQ ID NO:22). PCR was performed on a human fetal liver cDNA library (Marathon ready cDNA CLONTECH #7403-1) using Advantage Klen Taq Polymerase mix (CLONTECH #8417-1) in the buffer supplied at 94°C for
25 30s and 68°C for 3 min for 35 cycles followed by 68°C for 4 min and then stopping at 15°C. A standard PCR programme for the Perkin-Elmer GeneAmp PCT system 2400 thermal cycle was used. The PCR yielded a prominent product of approximately 560 base pairs (bp; SEQ ID
30 NO:18), which was radiolabelled with [³²P] dCTP using a random priming method (Amersham, RPN, 1607, Mega prime kit) and used to screen a human fetal kidney 5N-STRETCH PLUS cDNA library (CLONTECH #HL1150x). Library screens were performed using Rapid Hybridisation Buffer
35 (Amersham, RPN 1636) according to manufacturer's instructions and membranes washed at 65°C for 30 min in 0.1xSSC/0.1% (w/v) SDS. Two independent cDNA clones

were obtained as lambda phage and subsequently subcloned and sequenced. Both clones (HFK-63 and HFK-66) contained 1.4 kilobase (kb) inserts that showed sequence similarity with murine NR6. The sequence and
5 corresponding amino acid translation of HFK-66 is shown in SEQ ID NO:24.

The translation protein sequences of clone HFK-66 shows a high degree of sequence similarity with the mouse NR6.

10

OLIGONUCLEOTIDES

UP1: 5NTCC AGG CAG CGG TCG GGG GAC AAC 3N [SEQ ID NO:26]
LP1: 5N TTG CTC ACA TCG TCC ACC ACC TTC 3N [SEQ ID
NO:27]

15

EXAMPLE 9

Genomic Structure of Human NR6

Human genomic DNA clones encoding human NR6 was
20 isolated by screening a human genomic library (Lambda
FIXJII Stratagene 946203) with radiolabelled
oligonucleotides, 2199 and 2200 (see below). These
oligonucleotides were designed based on human ESTs
(Genbank Acc:R87407, Genbank Acc:H14009) that were
25 identified from databases searched with murine NR6.
Filters were hybridised overnight at 37°C in 6xSSC
containing 2 mg/ml bovine serum albumin, 2 mg/ml Ficoll,
2mg/ml polyvinylpyrrolidone, 100 mM ATP, 10 mg/ml tRNA,
2 mM sodium pyrophosphate, 2 mg/ml salmon sperm DNA,
30 0.1% (w/v) SDS and 200 mg/ml sodium azide and washed at
65°C in 6 x SSC/0.1% SDS. Five independent genomic
clones were obtained and sequenced. The extend of
sequence obtained has determined that the clones overlap
and exhibit a similar genomic structure to murine NR6.
35 Exon coding regions are almost identical over the region
covered by the genomic clones while intron coding
regions differ, although the size of the introns are

comparable. The extent of known overlap is shown in Fig. 5.

OLIGONUCLEOTIDES:

5

2199: 5N CCC ACG CTT CTC ATC GGA TTC TCC CTG 3N [SEQ ID NO:36]

2200: 5N CAG TCC ACA CTG TCC TCC ACT CGG TAG 3N [SEQ ID NO:37]

10

EXAMPLE 10

Northern Blot Analysis of Human NR6 mRNA Expression

15 Clontech Multiple Tissue Northern Blots (Human MTN Blot, CLONTECH #7760-1, Human MTN Blot IV, CLONTECH #7766-I, Human Brain MTN Blot II, CLONTECH #7755-1, Human Brain MTN Blot III, CLONTECH #7750) were probed with a
20 radiolabelled 3N human NR6 cDNA clone, HFK-66 (SEQ ID NO:24). The clone was labelled with [³²P] dCTP using a random priming method (Amersham, RPN 1607, Mega prime kit). Hybridisation was performed in Express
Hybridisation Solution (CLONTECH H50910) for 3 hours at 67°C and membranes were washed in 0.1xSSC/0.1% w/v SDS
25 at 50°C.

A 1.8 kb transcript was detected in a variety of human tissues encompassing reproductive, digestive and neural tissues. High levels were observed in the heart,
30 placenta, skeletal muscle, prostate and various areas of the brain, lower levels were observed in the testis, uterus, small intestine and colon. Photographs showing these Northern blots are available upon request. This
expression pattern differs from the expression pattern
35 observed with murine NR6.

EXAMPLE 11

Mouse NR6 Expression Vectors

pEF-FLAG/mNR6.1

5 The mature coding region of mouse NR6.1 was amplified using the PCR to introduce an in-frame Asc I restriction enzyme site at the 5' end of the mature coding region and an Mlu I site at the 3' end, using the following oligonucleotides:-

10

5N oligo 5N-AGCTGGCGCGCCTCCCGGGCGGATCGGGAGCCCAC-3N [SEQ ID NO:30]

3N oligo 5N-AGCTACGCGTTTAGAGTTTAGCCGGCAG-3N [SEQ ID NO:31]

15

The resulting PCR derived DNA fragment was then digested with Asc I and Mlu I and cloned into the Mlu I site of pEF-FLAG. Expression of NR6 is under the control of the polypeptide chain elongation factor 1 α promoter as described (16) and results in the secretion, using the IL3 signal sequence from pEF-FLAG, of N-terminal FLAG-tagged NR6 protein.

25 pEF-FLAG was generated by modifying the expression vector pEF-BOS as follows:-

pEF-BOS (16) was digested with Xba I and a linker was synthesized that encoded the mouse IL3 signal sequence (MVLASSTTSIH TMLLLLLMLFHLGLQASIS) and the FLAG epitope (DYKDDDDK). Asc I and Mlu I restriction enzyme sites were also introduced as cloning sites. The sequence of the linker is as follows:-

35 M
CTAGACTAGTGCTGACACAATGGTTCTTGCCAGCTCTACCACCAGCATCCACACCA
TG

TGATCACGACTGTGTTACCAAGAACGGTCGAGATGGTGGTCGTAGGTGTGGTAC

5 L L L L L M L F H L G L Q A S I S Asc
I
CTGCTCCTGCTCCTGATGCTCTTCCACCTGGGACTCCAAGCTTCAATCTCGGCGCG
CC
GACGAGGACGAGGACTAGCAGAAGGTGGACCCTGAGGTTCGAAGTTAGAGCCGCGC
GG

10 D Y K D D D D K Mlu I
AGGACTACAAGGACGACGATGACAAGACGCGTGCTAGCACTAGT

15 TCCTGATGTTCTGCTGCTACTGTTCTGCGCACGATCGTGATCAGATC

The two oligonucleotides were annealed together and
ligated into the Xba I site of pEF-BOS to give pEF-FLAG.

20 pCOS1/FLAG/mNR6 & pCHO1/FLAG/mNR6

A DNA fragment containing the sequences encoding IL3
signal sequence/Flag/mNR6 and the poly(A) adenylation
signal from human G-CSF cDNA, was excised from pEF-
FLAG/mNR6 using the restriction enzyme EcoR I. This DNA
25 fragment was then inserted into the EcoR I cloning site
of pCOS1 and pCHO1

30 The pCOS1 and pCHO1 vectors were constructed as follows.
pCHO1 is also described in reference (17) but with a
different selectable marker.

pCOS1 was prepared by digesting HEF-12h-g"1 (see Figure
24 of International Patent Publication No. WO 92/19759)
with EcoRI and SmaI and ligating the digesting product
35 iwht an EcoRI-NotI-BamHI adaptor (Takara 4510). The
resulting plasmid comprises an EFl" promoter/enhancer,
Nco^r marker gene, SV40E, ori and an Amp^r marker gene.

pCH01 was constructed by digesting DHFR-PMh-gr1 (see Figure 25 of International Patent Publication No. WO 92/19759) with PvuI and Eco47III and ligating same with pCOSI digested with PvuI and Eco47III. The resulting vector, pCH01, comprises an EFI" promoter/enhancer, an DHFR marker gene, SV40E, Ori and a Amp^r gene.

EXAMPLE 12

10

mRN6 has been expressed as an NN Flag tagged protein following transfection of CHO cells and as a CN Flag tagged protein following transfection of KUSA cells in both cases varying levels of dimeric and aggregated NR6 were secreted.

EXAMPLE 13

Murine NR6 expression

20

NR6 expression studies were conducted in murine Northern Blots. At the level of sensitivity used in the adult mouse, NR6 expression was detected in salivary gland, lung and testis. During embryonic development, NR6 is expressed in fetal tissues from day 10 of gestation through to birth. In cell lines, NR6 expression has been observed in the T-lymphoid line CTLL-2 as well as in FD-PyMT (FDC-P1 myeloid cells expressing polyoma midle T gene), and fibroblastoid cells including bone marrow and fetal liver stromal lines.

30

EXAMPLE 14

Expression, purification and characterisation of CHO and KUSA mNR6

35

The methods provide for the production of a dimeric form of CHO derived NN FLAG-mNR6 without refolding. All

other methods are capable of producing NR6 and are encompassed by the present invention.

A. Production of CHO derived N' FLAG-mNR6 (dimeric form)

(i) Protein Production

To analyse structure and functional activity, a cDNA fragment containing the entire coding sequence of murine NR6 with an N-terminal FLAG (NN FLAG) sequence was cloned into the EcoRI site of the expression vector pCHO1. For stable production of N-terminal FLAG-tagged NR6 the vector contains the DHFR (dihydrofolate reductase) gene as a selective marker with the NR6 gene under the control of an EF1a promoter. CHO cells were transfected with the construct using a polycationic liposome transfection reagent (Lipofectamine, GibcoBRL).

(ii) Lipofectamine transfection method

Using six well tissue culture plates either 2×10^5 KUSA cells in 2ml IMDM + 10% (v/v) FCS or 2×10^5 CHO cells were cultured in 2ml "-MEM + 10% (v/v) FCS until 70% confluent. 2Fg DNA diluted in 100Fl OPTI-MEM I (Gibco BRL, USA) was mixed gently with 12Fl lipofectamine diluted in 100Fl OPTI-MEM I and incubated at room temperature for 30min to allow DNA complex formation. DNA complexes were gently diluted in a total volume of 1ml of OPTI-MEM I and overlaid onto washed KUSA or CHO cell monolayers. A further 1ml IMDM + 20% (v/v) FCS (KUSA cells) or 1ml "-MEM + 20% (v/v) FCS (CHO cells) was added to transfected cells after 5 hours. At 24 hours, the culture medium was replaced with fresh complete growth medium. At 48 hours after transfection, selection was applied. A methotrexate resistant clone secreting comparatively high levels of NR6 was selected and expanded for further analysis.

(iii) Protein expression

CHO cells were grown to confluence in roller bottles in nucleoside free "-MEM + 10% (v/v) FCS. Selection was maintained by using 100 ng/ml Methotrexate in the conditioned media according to manufacturer instructions. Expression was monitored by Biosensor and harvesting found to be optimal at 3 to 4 days.

10 B. Protein Analysis

(i) Biosensor analysis

Expression and purification was monitored by Biosensor analysis (BiaCore™, Sweden) where anti FLAG peptide M2 antibody (Kodak Eastman, USA), specific for the FLAG peptide sequence was bound to the sensorchip. Fractions were analysed for binding to the sensor surface (resonance units) and the sample then removed from the surface using 50 mM Diethylamine pH 12.0 prior to analysis of the next fraction. Immobilisation and running conditions of the Biosensor follow the manufacturer's instructions.

25 (ii) Protein Production

In order to generate and characterise NR6, conditioned media (2 L) produced by CHO cells was harvested after day 3, post confluence. Conditioned media was concentrated using diafiltration with a 10,000 molecular weight cut-off. (Easy flow, Sartorius, Aus). At a volume of 200 ml (i.e. 10 x concentrated) the sample was buffer exchanged into 20 mM Tris, 0.15M NaCl, 0.02% (v/v) Tween 20 pH 7.5 (Buffer A).

35

(iii) Immunoprecipitation and Western Blot analysis of mNR6

Concentrated conditioned media (1ml) was immunoprecipitated with M2 affinity resin (20Fl, Kodak Eastman). To examine the structural characterisation of mNR6 SDS PAGE was performed under reducing and non-reducing conditions. Separation was performed on NOVEX 4-20% (v/v) Tris/glycine gradient gels and protein transferred on PVDF membrane. Western blots were probed with biotinylated M2 antibody (primary, 1:500) and then streptavidin peroxidase (secondary, 1:3000). Samples were visualised by autoradiography using electrochemiluminescence (ECL, Dupont, USA).

By regression analysis of prestained standards (BIORAD, Aus.) the molecular weight of the monomeric unit was calculated to be 65,000 daltons. Under non-reducing conditions the molecular weight was calculated to be 127,000 indicating that NR6 is a disulphide linked dimer. A tetrameric complex running at approximately 250,000 daltons was also observed. Although a band running at approximately 50,000 daltons was observed, no monomeric NR6 was detected under non-reducing conditions indicating that the majority of NR6 expressed in this system is disulphide linked.

(iv) Affinity Chromatography of mNR6

Concentrated conditioned media (200 ml) was applied to M2 affinity resin (5ml) under gravity. To enhance recovery the unbound fraction was reapplied to the column four times prior to extensive washing of the column with 200 volumes of Buffer A. Biosensor analysis indicates that approximately 20% of the M2 binding originally present in the concentrate remains in the unbound fraction. The bound fraction was eluted from the column using an immunodesorbant (50 ml); actisept (Sterogene Labs, USA).

(v) Ion exchange and Desalting of mNR6

In order to buffer exchange mNR6 prior to anion chromatography, 10 ml batches of the eluted fraction (50
5 ml) were applied to an XK column (400 x 26 mm I.D.) containing G25 sepharose (Pharmacia, Sweden). Chromatography was developed at 4 ml/min using an FPLC (Pharmacia, Sweden) equipped with an online UV280 and conductivity monitor. The mobile phase was 10 mM Tris,
10 0.1M NaCl, 0.02% v/v Tween, pH 8.0. 10 ml fractions were collected between 12.5 min and 25 min to optimise recovery and removal of salt. Fractions were analysed by Biosensor analysis and pooled according to binding.

15 All pooled active fractions were diluted with an equal volume of 20 mM Tris, 0.02% (v/v) Tween, pH 8.5 (Buffer B) and then loaded onto a Mono Q 5/5 (Pharmacia, Sweden) at a flow rate of 2 ml/min. The column was washed with buffer B. Elution was performed using a linear gradient
20 between buffer B and buffer B containing 0.6M NaCl over 30 min at a flow rate of 1 ml/min. Fractions (1 minute) were collected and analysed on the Biosensor and also by SDS PAGE and Western blot analysis. Fractions 15 to 26 (approximately 0.4M NaCl) appear to contain the majority
25 of mNR6 as indicated by the Biosensor.

C. Production of CHO derived N' FLAG-mNR6 (monomeric form)

30 (i) Protein Production

A cDNA fragment containing the entire coding sequence of murine NR6 with an N-terminal FLAGJ sequence was cloned into the expression vector pCHO1 for production of N-
35 terminal FLAG-tagged protein. This vector contains a neomycin resistance gene with expression of the NR6 gene under the control of an EF1" promoter. This expression

construct was transfected into CHO cells using Lipofectamine (Gibco BRL, USA) according to the manufacturer instructions. Transfected cells were cultured in IMDM + 10% (v/v) FCS with resistant cells
5 selected in geneticin (600Fg/ml, Gibco BRL, USA). A neomycin resistant clone, secreting comparatively high levels of NR6 was selected and expanded for further analysis.

10 (ii) Protein expression

N' FLAG-NR6 expressed in serum free conditioned media (10 litre) was harvested from transfected CHO and cells. Collected media was concentrated using a CH2
15 ultrafiltration system equipped with a S1Y10 cartridge (Amicon molecular weight cut-off 10,000). Preliminary examination of the expressed product under reducing and non-reducing SDS PAGE followed by western blot analysis was performed. Visualisation of the protein on Westerns
20 was specific to the primary antibody anti FLAG M2. Under reducing conditions a band approximately at 65,000 daltons was observed. Under non-reducing conditions, dimer and larger molecular weight aggregates were observed. These are disulphide linked monomers as they
25 are not present in the reducing gel. Small amounts of monomer appear to be present in non-reducing gels.

(iii) Affinity Chromatography of NR6

Concentrated conditioned media was applied to an anti
30 FLAG M2 affinity resin (100 x 16 mm I.D.). After washing the unbound proteins off the column, the bound proteins were eluted using FLAG peptide (60Fg/ml) in PBS.

35 (iv) Ion Exchange Chromatography of NR6

Eluted fractions from affinity column were dialysed overnight against 20 mM Tris-HCl pH 8.5 (buffer C)

containing 50 mM Dithiothreitol (DTT) using 25,000 cut-off dialysis tubing (Spectra/Por7, Spectrum). The dialysed fractions were loaded onto Mono Q 5/5 (Pharmacia, Sweden) previously equilibrated with buffer C containing 5 mM DTT. Chromatography was developed using a linear gradient between buffer C and buffer C containing 1.0 M NaCl at a flow rate of 0.5 ml / min.

(v) Refolding of NR6

Fractions containing NR6 from the Mono Q were adjusted to 50 mM DTT and left overnight at 41C. To initiated refolding the sample was then dialysed against 50 mM Tris-HCl (pH 8.5), 2 M Urea, 0.1% (v/v) Tween 20, 10 mM Glutathione (reduced) and 2 mM Glutathione (oxidised) at a final protein concentration of 100 Fg / ml. Folding was carried out at ambient temperature with one change of the buffer over 24 hours.

(v) Reversed Phase High Performance Liquid Chromatography (RP-HPLC)

The folded product was further purified by RP-HPLC using a Vydac C4 resin (250 x 4.6 mm I.D.) previously equilibrated with 0.1% (v/v) Trifluoroacetic acid (TFA). Elution was carried out using a linear gradient from 0 to 80% (v/v) acetonitrile / 0.1% (v/v) TFA at a flow rate of 1 ml per minute.

D. pCHO1/NR6/FLAG

In order to determine the native N termini of NR6, a C terminal FLAG NR6 CHO cell line was established.

The plasmid pKUSA166 (murine NR6 cDNA cloned into the EcoR I site of pBLUESCRIPT) was digested with BamH I to remove the sequences encoding the last 15 amino acids of murine NR6. Synthetic oligonucleotides which encode the

3' end of mouse NR6 followed by the FLAG peptide tag were annealed and ligated into the BamH I site of pKUSA166. The sequence of the oligonucleotides was as follows:-

5

I L P S G R R G A A R G P A G D Y K D
D D D K * [SEQ ID NO:34]
GATCTTGCCCTCGGGCAGACGGGGTGCGGCGAGAGGTCCTGCCGGCGACTACAAGG
10 ACGACGATGACAAGTA G [SEQ ID NO:33]
AACGGGAGCCCGTCTGCCCCACGCCGCTCTCCAGGACGGCCGCTGATGTTCTGCT
GCTACTGTTTCATCCTAG [SEQ ID NO:35]

15 The 5' end of the linker introduces a silent mutation (CTG > TTG), to destroy the 5' BamH I site upon insertion of the linker. The NR6 cDNA (with native signal sequence) with the C-terminal FLAG was cut out of pKUSA166 with EcoR I and BamH I and cloned into the EcoR I - BamH I cloning sites of pCHO-1. This vector results
20 in the secretion of NR6 protein with a C-terminal flag tag (CN FLAG-mRN6).

This vector results in the secretion of NR6 protein from KUSA cells. The vector pCHO1 has been previously
25 described in (17) although with a different secretable marker.

(i) Production of polyclonal NR6 antiserum

30 The following peptide from the N terminal area of NR6 was chosen for production of polyclonal antiserum to NR6

VISPQDPTLLIGSSLQATCSIHGDTP [SEQ ID NO:39]

35 The peptide was conjugated to KLH and injected into rabbits. Production and purification of the polyclonal antibody specific to the NR6 peptide sequence follows

standard methods.

(ii) Protein expression

5 KUSA cells transfected with cDNA of C terminal tagged mNR6 were grown to confluence in flasks (800ml) using IMDM media containing 10% (v/v) FBS. Conditioned media (100 ml) was harvested 3 -4 days post confluence.

10 (iii) Characterisation of NR6 by Immunoprecipitation and Western blotting

In order to establish that NR6 with the predicted sequence is produced in KUSA cells transfected with the
15 cDNA, western blot analysis using both M2 antibody and purified NR6 specific rabbit antibody were performed. Conditioned media (1 to 5 ml) was immunoprecipitated with M2 affinity resin (10-20 Fl). Then after sufficient time for binding, the beads were washed with MT-PBS and
20 subsequently NR6 eluted with 100 Fg/ml FLAG peptide (40 Fl, (1, 5 minute incubation). The sample was then subjected to reducing and non reducing SDS PAGE followed by western blot analysis. Both purified NR6 polyclonal antibody (purified by protein G) and M2 antibody
25 recognise a band under reducing conditions of a molecular weight size approximately 65,000 daltons. Since the two antibodies recognising resides at the N terminus and C terminus it is reasonable to assume that full length NR6 is produced. Biotinylation of the
30 respective antibodies by standard methods reduces the background. Under non-reducing conditions polyclonal NR6 bind antibodies to a band of a molecular weight of approximately 127,000, consistent with a dimeric NR6 disulphide linked form. Minor components of tetrameric
35 NR6 are present, no monomeric NR6 is evident using polyclonal NR6 antibodies.

EXAMPLE 15

Generation of NR6 knockout mice

To construct the NR6 targeting vector, 4.1kb of genomic NR6 DNA containing exons 2 through to 6 was deleted and replaced with G418-resistance cassette, leaving 5N and 3N NR6 arms of 2.9 and 4.5 kb respectively. A 4.5 kb XhoI fragment of the murine genomic NR6 clone 2.2 (Figure 3) containing exons 7, 8 and 3N flanking sequence was subcloned into the XhoI site of pBluescript generating pBSNR6Xho4.5. A 2.9kb NotI-StuI fragment within NR6 intron 1 from the same genomic clone was inserted into NotI and EcoRV digested pBSNR6Xho4.5 creating pNR6-Ex2-6. This plasmid was digested with ClaI, which was situated between the two NR6 fragments, and following blunt ending, ligated with a blunted 6kb HindIII fragment from placZneo, which contains the lacZgene and a PGKneo cassette, to generate the final targeting vector, pNR6lacZneo. pNR6lacZneo was linearised with NotI and electroporated into W9.5 embryonic stem cells. After 48 hours, transfected cells were selected in 175 Fg/ml G418 and resistant clones picked and expanded after a further 8 days.

Clones in which the targetting vector had recombined with the endogenous NR6 gene were identified by hybridising SpeI-digested genomic DNA with a 0.6 kb XhoI-StuI fragment from genomic NR6 clone 2.2. This probe (probe A, Figure 4), which is located 3N to the NR6 sequences in the targeting vector, distinguished between the endogenous (9.9 kb) and targeted (7.1 kb) NR6 loci (Figure 5).

Genomic DNA was digested with SpeI for 16hrs at 37°C, electrophoresed through 0.8% (w/v) agarose, transferred to nylon membranes and hybridised to ³²P-labelled probe in a solution containing 0.5M sodium phosphate, 7% (w/v)

SDS, 1mM EDTA and washed in a solution containing 40mM sodium phosphate, 1% (w/v) SDS at 65°C. Hybridising bands were visualised by autoradiography for 16 hours at -70°C using Kodak XAR-5 film and intensifying screens.

5 Two targeted ES cell clones, W9.5NR6-2-44 and W9.5NR6-4-2, were injected into C57Bl/6 blastocysts to generate chimeric mice. Male chimeras were mated with C57Bl/6 females to yield NR6 heterozygotes which were subsequently interbred to produce wild-type (NR6^{+/+}),

10 heterozygous (NR6^{+/-}) and mutant (NR6^{-/-}) mice. The genotypes of offspring were determined by Southern Blot analysis of genomic DNA extracted from tail biopsies.

Genotyping of mice at weaning from matings between NR6^{+/-} heterozygous mice derived from both targeted ES cell clones revealed an absence of homozygous NR6^{-/-} mutants. As no unusual loss of mice was observed between birth and weaning, this suggests that lack of NR6 is lethal during embryonic development or immediately after birth.

20 Genotyping of embryonic tissues at various stages of development suggests that death occurs late in gestation (beyond day 16) or at birth.

EXAMPLE 16

25 Oligonucleotides

1943:

5' GTC CAA GTG CGT TGT AAC CCA 3'

2070:

5' GCT GAG TGT GCG CTG GGT CTC ACC 3'

30 2057:

5' GGC TCC ACT CGC TCC AGA 3'

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically

35 described. It is to be understood that the invention includes all such variations and modifications. The

invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said
5 steps or features.

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SEQUENCE LISTING

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RECEPTOR AND GENETIC
15 SEQUENCES ENCODING SAME

(iii) NUMBER OF SEQUENCES: 39

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25 (F) ZIP: 3000

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
30 (C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version

#1.25

(vi) CURRENT APPLICATION DATA:

35 (A) APPLICATION NUMBER:
PCT INTERNATIONAL APPLICATION

(B) FILING DATE: 11-SEP-1997

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(A) APPLICATION NUMBER: PO2246/96

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(B) FILING DATE: 11-SEP-1996

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15

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 5 amino acids

(B) TYPE: amino acid

20

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

25

Trp Ser Xaa Trp Ser

30

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: base pairs

(B) TYPE: nucleic acid

35

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

5

ACTCGCTCCA GATTCCCGCC TTTT

24

10 (2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs

(B) TYPE: nucleic acid

15 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

25 TCCCGCCTTT TTCGACCCAT AGAT

24

(2) INFORMATION FOR SEQ ID NO:4:

30 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

35

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

GGTACTTGGC TTGGAAGAGG AAAT

24

(2) INFORMATION FOR SEQ ID NO:5:

5

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

10

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CGGCTCACGT GCACGTCGGG TGGG

24

(2) INFORMATION FOR SEQ ID NO:6:

20

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

25

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

AGCTGCTGTT AAAGGGCTTC TC

22

35

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Oligonucleotide

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

(A/G)CTCCA(A/G)TC(A/G) CTCCA

15

15

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Oligonucleotide

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

30 (A/G)CTCCA(C/T)TC(A/G) CTCCA

15

35

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 base pairs

- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

5 (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:
10

AAGTGTGACC ATCATGTGGA C 21

15 (2) INFORMATION FOR SEQ ID NO:10:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 18 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- 20

(ii) MOLECULE TYPE: DNA
25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

30 GGAGGTGTTA AGGAGGCG 18

(2) INFORMATION FOR SEQ ID NO:11:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 18 base pairs
 - (B) TYPE: nucleic acid
- 35

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

10

ATGCCCCGCGG GTCGCCCCG

18

15 (2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1506 base pairs

(B) TYPE: nucleic acid

20 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

25

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..1242

30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

GGCACGAGCT TCGCTGTCCG CGCCCAGTGA CGCGCGTGCG GACCCGAGCC CCAATCTGCA -64
35 CCCC GCAGAC TCGCCCCCGC CCCATACCGG CGTTGCAGTC ACCGCCCGTT GCGCGCCACC -4
CCC -3
ATG CCC GCG GGT CGC CCG GGC CCC GTC GCC CAA TCC GCG CGG CGG CCG 48

- 77 -

SUBSTITUTE SHEET (RULE 26)

	Met	Pro	Ala	Gly	Arg	Pro	Gly	Pro	Val	Ala	Gln	Ser	Ala	Arg	Arg	Pro	
	1				5				10					15			
	CCG	CGG	CCG	CTG	TCC	TCG	CTG	TGG	TCG	CCT	CTG	TTG	CTC	TGT	GTC	CTC	96
5	Pro	Arg	Pro	Leu	Ser	Ser	Leu	Trp	Ser	Pro	Leu	Leu	Leu	Cys	Val	Leu	
				20				25					30				
	GGG	GTG	CCT	CGG	GGC	GGA	TCG	GGA	GCC	CAC	ACA	GCT	GTA	ATC	AGC	CCC	144
	Gly	Val	Pro	Arg	Gly	Gly	Ser	Gly	Ala	His	Thr	Ala	Val	Ile	Ser	Pro	
10			35					40					45				
	CAG	GAC	CCC	ACC	CTT	CTC	ATC	GGC	TCC	TCC	CTG	CAA	GCT	ACC	TGC	TCT	192
	Gln	Asp	Pro	Thr	Leu	Leu	Ile	Gly	Ser	Ser	Leu	Gln	Ala	Thr	Cys	Ser	
		50					55				60						
15																	
	ATA	CAT	GGA	GAC	ACA	CCT	GGG	GCC	ACC	GCT	GAG	GGG	CTC	TAC	TGG	ACC	240
	Ile	His	Gly	Asp	Thr	Pro	Gly	Ala	Thr	Ala	Glu	Gly	Leu	Tyr	Trp	Thr	
	65					70				75				80			
20	CTC	AAT	GGT	CGC	CGC	CTG	CCC	TCT	GAG	CTG	TCC	CGC	CTC	CTT	AAC	ACC	288
	Leu	Asn	Gly	Arg	Arg	Leu	Pro	Ser	Glu	Leu	Ser	Arg	Leu	Leu	Asn	Thr	
					85					90				95			
	TCC	ACC	CTG	GCC	CTG	GCC	CTG	GCT	AAC	CTT	AAT	GGG	TCC	AGG	CAG	CAG	336
25	Ser	Thr	Leu	Ala	Leu	Ala	Leu	Ala	Asn	Leu	Asn	Gly	Ser	Arg	Gln	Gln	
				100					105				110				
	TCA	GGA	GAC	AAT	CTG	GTG	TGT	CAC	GCC	CGA	GAC	GGC	AGC	ATT	CTG	GCT	384
	Ser	Gly	Asp	Asn	Leu	Val	Cys	His	Ala	Arg	Asp	Gly	Ser	Ile	Leu	Ala	
30			115					120				125					
	GGC	TCC	TGC	CTC	TAT	GTT	GGC	TTG	CCC	CCT	GAG	AAG	CCC	TTT	AAC	ATC	432
	Gly	Ser	Cys	Leu	Tyr	Val	Gly	Leu	Pro	Pro	Glu	Lys	Pro	Phe	Asn	Ile	
		130					135					140					
35																	

	AGC TGC TGG TCC CGG AAC ATG AAG GAT CTC ACG TGC CGC TGG ACA CCG	480
	Ser Cys Trp Ser Arg Asn Met Lys Asp Leu Thr Cys Arg Trp Thr Pro	
	145 150 155 160	
5	GGT GCA CAC GGG GAG ACA TTC TTA CAT ACC AAC TAC TCC CTC AAG TAC	528
	Gly Ala His Gly Glu Thr Phe Leu His Thr Asn Tyr Ser Leu Lys Tyr	
	165 170 175	
10	AAG CTG AGG TGG TAC GGT CAG GAT AAC ACA TGT GAG GAG TAC CAC ACT	576
	Lys Leu Arg Trp Tyr Gly Gln Asp Asn Thr Cys Glu Glu Tyr His Thr	
	180 185 190	
15	GTG GGC CCT CAC TCA TGC CAT ATC CCC AAG GAC CTG GCC CTC TTC ACT	624
	Val Gly Pro His Ser Cys His Ile Pro Lys Asp Leu Ala Leu Phe Thr	
	195 200 205	
20	CCC TAT GAG ATC TGG GTG GAA GCC ACC AAT CGC CTA GGC TCA GCA AGA	672
	Pro Tyr Glu Ile Trp Val Glu Ala Thr Asn Arg Leu Gly Ser Ala Arg	
	210 215 220	
25	TCT GAT GTC CTC ACA CTG GAT GTC CTG GAC GTG GTG ACC ACG GAC CCC	720
	Ser Asp Val Leu Thr Leu Asp Val Leu Asp Val Val Thr Thr Asp Pro	
	225 230 235 240	
30	CCA CCC GAC GTG CAC GTG AGC CGC GTT GGG GGC CTG GAG GAC CAG CTG	768
	Pro Pro Asp Val His Val Ser Arg Val Gly Gly Leu Glu Asp Gln Leu	
	245 250 255	
35	AGT GTG CGC TGG GTC TCA CCA CCA GCT CTC AAG GAT TTC CTC TTC CAA	816
	Ser Val Arg Trp Val Ser Pro Pro Ala Leu Lys Asp Phe Leu Phe Gln	
	260 265 270	
40	GCC AAG TAC CAG ATC CGC TAC CGC GTG GAG GAC AGC GTG GAC TGG AAG	864
	Ala Lys Tyr Gln Ile Arg Tyr Arg Val Glu Asp Ser Val Asp Trp Lys	
	275 280 285	

GTG GTG GAT GAC GTC AGC AAC CAG ACC TCC TGC CGT CTC GCG GGC CTG 912
 Val Val Asp Asp Val Ser Asn Gln Thr Ser Cys Arg Leu Ala Gly Leu
 290 295 300

5 AAG CCC GGC ACC GTT TAC TTC GTC CAA GTG CGT TGT AAC CCA TTC GGG 960
 Lys Pro Gly Thr Val Tyr Phe Val Gln Val Arg Cys Asn Pro Phe Gly
 305 310 315 320

10 ATC TAT GGG TCG AAA AAG GCG GGA ATC TGG AGC GAG TGG AGC CAC CCC 1008
 Ile Tyr Gly Ser Lys Lys Ala Gly Ile Trp Ser Glu Trp Ser His Pro
 325 330 335

15 ACC GCT GCC TCC ACC CCT CGA AGT GAG CGC CCG GGC CCG GGC GGC GGC 1056
 Thr Ala Ala Ser Thr Pro Arg Ser Glu Arg Pro Gly Pro Gly Gly Gly
 340 345 350

20 GTG TGC GAG CCG CGG GGC GGC GAG CCC AGC TCG GGC CCG GTG CGG CGC 1104
 Val Cys Glu Pro Arg Gly Gly Glu Pro Ser Ser Gly Pro Val Arg Arg
 355 360 365

GAG CTC AAG CAG TTC CTC GGC TGG CTC AAG AAG CAC GCA TAC TGC TCG 1152
 Glu Leu Lys Gln Phe Leu Gly Trp Leu Lys Lys His Ala Tyr Cys Ser
 370 375 380

25 AAC CTT AGT TTC CGC CTG TAC GAC CAG TGG CGT GCT TGG ATG CAG AAG 1200
 Asn Leu Ser Phe Arg Leu Tyr Asp Gln Trp Arg Ala Trp Met Gln Lys
 385 390 395 400

30 TCA CAC AAG ACC CGA AAC CAG GTC CTG CCG GCT AAA CTC TAAGGATAGG 1249
 Ser His Lys Thr Arg Asn Gln Val Leu Pro Ala Lys Leu
 405 410

CCATCCTCCT GCTGGGTCAG ACCTGGAGGC TCACCTGAAT TGGAGCCCCT CTGTACCATC 1309

35 TGGGCAACAA AGAAACCTAC CAGAGGCTGG GGCACAATGA GCTCCACAA CCACAGCTTT 1369

GGTCCACATG ATGGTCACAC TTGGATATAC CCCAGTGTGG GTAAGGTTGG GGTATTGCAG 1429

GGCCTCCCAA CAATCTCTTT AAATAAATAA AGGAGTTGTT CAGGTAAAAA AAAAAAAAAA 1489
 AAAAAAAAAA AAAAAA 1506

5

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 413 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

10

(ii) MOLECULE TYPE: protein

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Met Pro Ala Gly Arg Pro Gly Pro Val Ala Gln Ser Ala Arg Arg Pro
 1 5 10 15

Pro Arg Pro Leu Ser Ser Leu Trp Ser Pro Leu Leu Leu Cys Val Leu
 20 25 30

Gly Val Pro Arg Gly Gly Ser Gly Ala His Thr Ala Val Ile Ser Pro
 35 40 45

Gln Asp Pro Thr Leu Leu Ile Gly Ser Ser Leu Gln Ala Thr Cys Ser
 50 55 60

Ile His Gly Asp Thr Pro Gly Ala Thr Ala Glu Gly Leu Tyr Trp Thr
 30 65 70 75 80

Leu Asn Gly Arg Arg Leu Pro Ser Glu Leu Ser Arg Leu Leu Asn Thr
 85 90 95

Ser Thr Leu Ala Leu Ala Leu Ala Asn Leu Asn Gly Ser Arg Gln Gln
 35 100 105 110

	Ser Gly Asp Asn Leu Val Cys His Ala Arg Asp Gly Ser Ile Leu Ala	
	115	120 125
5	Gly Ser Cys Leu Tyr Val Gly Leu Pro Pro Glu Lys Pro Phe Asn Ile	
	130	135 140
	Ser Cys Trp Ser Arg Asn Met Lys Asp Leu Thr Cys Arg Trp Thr Pro	
	145	150 155 160
10	Gly Ala His Gly Glu Thr Phe Leu His Thr Asn Tyr Ser Leu Lys Tyr	
	165	170 175
	Lys Leu Arg Trp Tyr Gly Gln Asp Asn Thr Cys Glu Glu Tyr His Thr	
	180	185 190
15	Val Gly Pro His Ser Cys His Ile Pro Lys Asp Leu Ala Leu Phe Thr	
	195	200 205
	Pro Tyr Glu Ile Trp Val Glu Ala Thr Asn Arg Leu Gly Ser Ala Arg	
20	210	215 220
	Ser Asp Val Leu Thr Leu Asp Val Leu Asp Val Val Thr Thr Asp Pro	
	225	230 235 240
25	Pro Pro Asp Val His Val Ser Arg Val Gly Gly Leu Glu Asp Gln Leu	
	245	250 255
	Ser Val Arg Trp Val Ser Pro Pro Ala Leu Lys Asp Phe Leu Phe Gln	
	260	265 270
30	Ala Lys Tyr Gln Ile Arg Tyr Arg Val Glu Asp Ser Val Asp Trp Lys	
	275	280 285
	Val Val Asp Asp Val Ser Asn Gln Thr Ser Cys Arg Leu Ala Gly Leu	
35	290	295 300

Lys Pro Gly Thr Val Tyr Phe Val Gln Val Arg Cys Asn Pro Phe Gly
 305 310 315 320
 Ile Tyr Gly Ser Lys Lys Ala Gly Ile Trp Ser Glu Trp Ser His Pro
 5 325 330 335
 Thr Ala Ala Ser Thr Pro Arg Ser Glu Arg Pro Gly Pro Gly Gly Gly
 340 345 350
 Val Cys Glu Pro Arg Gly Gly Glu Pro Ser Ser Gly Pro Val Arg Arg
 10 355 360 365
 Glu Leu Lys Gln Phe Leu Gly Trp Leu Lys Lys His Ala Tyr Cys Ser
 370 375 380
 Asn Leu Ser Phe Arg Leu Tyr Asp Gln Trp Arg Ala Trp Met Gln Lys
 15 385 390 395 400
 Ser His Lys Thr Arg Asn Gln Val Leu Pro Ala Lys Leu
 20 405 410

(2) INFORMATION FOR SEQ ID NO:14:

25

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1549 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 30 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

35

(ix) FEATURE:

- (A) NAME/KEY: CDS
 (B) LOCATION: 1..1278

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

5 GGCACGAGCT TCGCTGTCCG CGCCCAGTGA CGCGCGTGCG GACCCGAGCC CCAATCTGCA -65
 CCCC GCAGAC TCGCCCCCGC CCCATACCGG CGTTGCAGTC ACCGCCCCGT GCGCGCCACC -5
 CCCA -1
 10 ATG CCC GCG GGT CGC CCG GGC CCC GTC GCC CAA TCC GCG CGG CGG CCG 48
 Met Pro Ala Gly Arg Pro Gly Pro Val Ala Gln Ser Ala Arg Arg Pro
 1 5 10 15
 15 CCG CGG CCG CTG TCC TCG CTG TGG TCG CCT CTG TTG CTC TGT GTC CTC 96
 Pro Arg Pro Leu Ser Ser Leu Trp Ser Pro Leu Leu Leu Cys Val Leu
 20 25 30
 20 GGG GTG CCT CGG GGC GGA TCG GGA GCC CAC ACA GCT GTA ATC AGC CCC 144
 Gly Val Pro Arg Gly Gly Ser Gly Ala His Thr Ala Val Ile Ser Pro
 35 40 45
 25 CAG GAC CCC ACC CTT CTC ATC GGC TCC TCC CTG CAA GCT ACC TGC TCT 192
 Gln Asp Pro Thr Leu Leu Ile Gly Ser Ser Leu Gln Ala Thr Cys Ser
 50 55 60
 30 ATA CAT GGA GAC ACA CCT GGG GCC ACC GCT GAG GGG CTC TAC TGG ACC 240
 Ile His Gly Asp Thr Pro Gly Ala Thr Ala Glu Gly Leu Tyr Trp Thr
 65 70 75 80
 35 CTC AAT GGT CGC CGC CTG CCC TCT GAG CTG TCC CGC CTC CTT AAC ACC 288
 Leu Asn Gly Arg Arg Leu Pro Ser Glu Leu Ser Arg Leu Leu Asn Thr
 85 90 95
 40 TCC ACC CTG GCC CTG GCC CTG GCT AAC CTT AAT GGG TCC AGG CAG CAG 336
 Ser Thr Leu Ala Leu Ala Leu Ala Asn Leu Asn Gly Ser Arg Gln Gln
 100 105 110

	TCA GGA GAC AAT CTG GTG TGT CAC GCC CGA GAC GGC AGC ATT CTG GCT	384
	Ser Gly Asp Asn Leu Val Cys His Ala Arg Asp Gly Ser Ile Leu Ala	
	115 120 125	
5	GGC TCC TGC CTC TAT GTT GGC TTG CCC CCT GAG AAG CCC TTT AAC ATC	432
	Gly Ser Cys Leu Tyr Val Gly Leu Pro Pro Glu Lys Pro Phe Asn Ile	
	130 135 140	
10	AGC TGC TGG TCC CGG AAC ATG AAG GAT CTC ACG TGC CGC TGG ACA CCG	480
	Ser Cys Trp Ser Arg Asn Met Lys Asp Leu Thr Cys Arg Trp Thr Pro	
	145 150 155 160	
15	GGT GCA CAC GGG GAG ACA TTC TTA CAT ACC AAC TAC TCC CTC AAG TAC	528
	Gly Ala His Gly Glu Thr Phe Leu His Thr Asn Tyr Ser Leu Lys Tyr	
	165 170 175	
20	AAG CTG AGG TGG TAC GGT CAG GAT AAC ACA TGT GAG GAG TAC CAC ACT	576
	Lys Leu Arg Trp Tyr Gly Gln Asp Asn Thr Cys Glu Glu Tyr His Thr	
	180 185 190	
25	GTG GGC CCT CAC TCA TGC CAT ATC CCC AAG GAC CTG GCC CTC TTC ACT	624
	Val Gly Pro His Ser Cys His Ile Pro Lys Asp Leu Ala Leu Phe Thr	
	195 200 205	
30	CCC TAT GAG ATC TGG GTG GAA GCC ACC AAT CGC CTA GGC TCA GCA AGA	672
	Pro Tyr Glu Ile Trp Val Glu Ala Thr Asn Arg Leu Gly Ser Ala Arg	
	210 215 220	
35	TCT GAT GTC CTC ACA CTG GAT GTC CTG GAC GTG GTG ACC ACG GAC CCC	720
	Ser Asp Val Leu Thr Leu Asp Val Leu Asp Val Val Thr Thr Asp Pro	
	225 230 235 240	
40	CCA CCC GAC GTG CAC GTG AGC CGC GTT GGG GGC CTG GAG GAC CAG CTG	768
	Pro Pro Asp Val His Val Ser Arg Val Gly Gly Leu Glu Asp Gln Leu	
	245 250 255	

	AGT GTG CGC TGG GTC TCA CCA CCA GCT CTC AAG GAT TTC CTC TTC CAA	816
	Ser Val Arg Trp Val Ser Pro Pro Ala Leu Lys Asp Phe Leu Phe Gln	
	260 265 270	
5	GCC AAG TAC CAG ATC CGC TAC CGC GTG GAG GAC AGC GTG GAC TGG AAG	864
	Ala Lys Tyr Gln Ile Arg Tyr Arg Val Glu Asp Ser Val Asp Trp Lys	
	275 280 285	
10	GTG GTG GAT GAC GTC AGC AAC CAG ACC TCC TGC CGT CTC GCG GGC CTG	912
	Val Val Asp Asp Val Ser Asn Gln Thr Ser Cys Arg Leu Ala Gly Leu	
	290 295 300	
15	AAG CCC GGC ACC GTT TAC TTC GTC CAA GTG CGT TGT AAC CCA TTC GGG	960
	Lys Pro Gly Thr Val Tyr Phe Val Gln Val Arg Cys Asn Pro Phe Gly	
	305 310 315 320	
20	ATC TAT GGG TCG AAA AAG GCG GGA ATC TGG AGC GAG TGG AGC CAC CCC	1008
	Ile Tyr Gly Ser Lys Lys Ala Gly Ile Trp Ser Glu Trp Ser His Pro	
	325 330 335	
	ACC GCT GCC TCC ACC CCT CGA AGT GAG CGC CCG GGC CCG GGC GGC GGG	1056
	Thr Ala Ala Ser Thr Pro Arg Ser Glu Arg Pro Gly Pro Gly Gly Gly	
	340 345 350	
25	GTG TGC GAG CCG CGG GGC GGC GAG CCC AGC TCG GGC CCG GTG CGG CGC	1104
	Val Cys Glu Pro Arg Gly Gly Glu Pro Ser Ser Gly Pro Val Arg Arg	
	355 360 365	
30	GAG CTC AAG CAG TTC CTC GGC TGG CTC AAG AAG CAC GCA TAC TGC TCG	1152
	Glu Leu Lys Gln Phe Leu Gly Trp Leu Lys Lys His Ala Tyr Cys Ser	
	370 375 380	
35	AAC CTT AGT TTC CGC CTG TAC GAC CAG TGG CGT GCT TGG ATG CAG AAG	1200
	Asn Leu Ser Phe Arg Leu Tyr Asp Gln Trp Arg Ala Trp Met Gln Lys	
	385 390 395 400	

TCA CAC AAG ACC CGA AAC CAG GAC GAG GGG ATC CTG CCT TCG GGC AGA 1248
 Ser His Lys Thr Arg Asn Gln Asp Glu Gly Ile Leu Pro Ser Gly Arg
 405 410 415

5 CGG GGT GCG GCG AGA GGT CCT GCC GGT TAAACTCTAA GGATAGGCCA 1295
 Arg Gly Ala Ala Arg Gly Pro Ala Gly
 420 425

TCCTCCTGCT GGGTCAGACC TGGAGGCTCA CCTGAATTGG AGCCCCTCTG TACCATCTGG 1355
 10 GCAACAAAGA AACCTACCAG AGGCTGGGGC ACAATGAGCT CCCACAACCA CAGCTTTGGT 1415
 CCACATGATG GTCACACTTG GATATACCCC AGTGTGGGTA AGGTTGGGGT ATTGCAGGGC 1475
 15 CTCCCAACAA TCTCTTTAAA TAAATAAAGG AGTTGTTCAG GTAAAAA AAAA 1535
 AAAAAAAAAA AAAA 1549

20

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 425 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

25

(ii) MOLECULE TYPE: protein

30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Met Pro Ala Gly Arg Pro Gly Pro Val Ala Gln Ser Ala Arg Arg Pro
 1 5 10 15

Pro Arg Pro Leu Ser Ser Leu Trp Ser Pro Leu Leu Leu Cys Val Leu
 20 25 30

35

	Gly Val Pro Arg Gly Gly Ser Gly Ala His Thr Ala Val Ile Ser Pro	
	35	40 45
5	Gln Asp Pro Thr Leu Leu Ile Gly Ser Ser Leu Gln Ala Thr Cys Ser	
	50	55 60
	Ile His Gly Asp Thr Pro Gly Ala Thr Ala Glu Gly Leu Tyr Trp Thr	
	65	70 75 80
10	Leu Asn Gly Arg Arg Leu Pro Ser Glu Leu Ser Arg Leu Leu Asn Thr	
	85	90 95
	Ser Thr Leu Ala Leu Ala Leu Ala Asn Leu Asn Gly Ser Arg Gln Gln	
	100	105 110
15	Ser Gly Asp Asn Leu Val Cys His Ala Arg Asp Gly Ser Ile Leu Ala	
	115	120 125
	Gly Ser Cys Leu Tyr Val Gly Leu Pro Pro Glu Lys Pro Phe Asn Ile	
20	130	135 140
	Ser Cys Trp Ser Arg Asn Met Lys Asp Leu Thr Cys Arg Trp Thr Pro	
	145	150 155 160
25	Gly Ala His Gly Glu Thr Phe Leu His Thr Asn Tyr Ser Leu Lys Tyr	
	165	170 175
	Lys Leu Arg Trp Tyr Gly Gln Asp Asn Thr Cys Glu Glu Tyr His Thr	
	180	185 190
30	Val Gly Pro His Ser Cys His Ile Pro Lys Asp Leu Ala Leu Phe Thr	
	195	200 205
	Pro Tyr Glu Ile Trp Val Glu Ala Thr Asn Arg Leu Gly Ser Ala Arg	
35	210	215 220

	Ser Asp Val Leu Thr Leu Asp Val Leu Asp Val Val Thr Thr Asp Pro		
	225	230	235 240
5	Pro Pro Asp Val His Val Ser Arg Val Gly Gly Leu Glu Asp Gln Leu	245	250 255
	Ser Val Arg Trp Val Ser Pro Pro Ala Leu Lys Asp Phe Leu Phe Gln	260	265 270
10	Ala Lys Tyr Gln Ile Arg Tyr Arg Val Glu Asp Ser Val Asp Trp Lys	275	280 285
	Val Val Asp Asp Val Ser Asn Gln Thr Ser Cys Arg Leu Ala Gly Leu	290	295 300
15	Lys Pro Gly Thr Val Tyr Phe Val Gln Val Arg Cys Asn Pro Phe Gly	305	310 315 320
	Ile Tyr Gly Ser Lys Lys Ala Gly Ile Trp Ser Glu Trp Ser His Pro	325	330 335
20	Thr Ala Ala Ser Thr Pro Arg Ser Glu Arg Pro Gly Pro Gly Gly Gly	340	345 350
	Val Cys Glu Pro Arg Gly Gly Glu Pro Ser Ser Gly Pro Val Arg Arg	355	360 365
	Glu Leu Lys Gln Phe Leu Gly Trp Leu Lys Lys His Ala Tyr Cys Ser	370	375 380
30	Asn Leu Ser Phe Arg Leu Tyr Asp Gln Trp Arg Ala Trp Met Gln Lys	385	390 395 400
	Ser His Lys Thr Arg Asn Gln Asp Glu Gly Ile Leu Pro Ser Gly Arg	405	410 415
35			

Arg Gly Ala Ala Arg Gly Pro Ala Gly

420

425

5

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 938 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

15

(ix) FEATURE:

- (A) NAME/KEY: CDS
 (B) LOCATION: 1..468

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

25	GGC ACC GTT TAC TTC GTC CAA GTG CGT TGT AAC CCA TTC GGG ATC TAT	48
	Gly Thr Val Tyr Phe Val Gln Val Arg Cys Asn Pro Phe Gly Ile Tyr	
	1 5 10 15	
	GGG TCG AAA AAG GCG GGA ATC TGG AGC GAG TGG AGC CAC CCC ACC GCT	96
30	Gly Ser Lys Lys Ala Gly Ile Trp Ser Glu Trp Ser His Pro Thr Ala	
	20 25 30	
	GCC TCC ACC CCT CGA AGT GAG CGC CCG GGC CCG GGC GGC GGG GTG TGC	144
	Ala Ser Thr Pro Arg Ser Glu Arg Pro Gly Pro Gly Gly Val Cys	
35	35 40 45	

	GAG CCG CGG GGC GGC GAG CCC AGC TCG GGC CCG GTG CGG CGC GAG CTC	192
	Glu Pro Arg Gly Gly Glu Pro Ser Ser Gly Pro Val Arg Arg Glu Leu	
	50 55 60	
5	AAG CAG TTC CTC GGC TGG CTC AAG AAG CAC GCA TAC TGC TCG AAC CTT	240
	Lys Gln Phe Leu Gly Trp Leu Lys Lys His Ala Tyr Cys Ser Asn Leu	
	65 70 75 80	
10	AGT TTC CGC CTG TAC GAC CAG TGG CGT GCT TGG ATG CAG AAG TCA CAC	288
	Ser Phe Arg Leu Tyr Asp Gln Trp Arg Ala Trp Met Gln Lys Ser His	
	85 90 95	
15	AAG ACC CGA AAC CAG GTA GGA AAG TTG GGG GAG GCT TGC GTG GGG GGT	336
	Lys Thr Arg Asn Gln Val Gly Lys Leu Gly Glu Ala Cys Val Gly Gly	
	100 105 110	
20	AAA GGA GCA GAG GAA GAG AGA GAC CCG GGT GAG CAG CCT CCA CAA CAC	384
	Lys Gly Ala Glu Glu Glu Arg Asp Pro Gly Glu Gln Pro Pro Gln His	
	115 120 125	
25	CGC ACT CTT CTT TCC AAG CAC AGG ACG AGG GGA TCC TGC CCT CGG GCA	432
	Arg Thr Leu Leu Ser Lys His Arg Thr Arg Gly Ser Cys Pro Arg Ala	
	130 135 140	
30	GAC GGG GTG CGG CGA GAG GTA AGG GGG TCT GGG TGAGTGGGGC CTACAGCAGT	485
	Asp Gly Val Arg Arg Glu Val Arg Gly Ser Gly	
	145 150 155	
35	CTAGATGAGG CCCTTTCCCC TCCTTCGGTG TTGCTCAAAG GGATCTCTTA GTGCTCATTT	545
	CACCCACTGC AAAGAGCCCC AGGTTTACT GCATCATCAA GTTGCTGAAG GGTCCAGGCT	605
	TAATGTGGCC TCTTTTCTGC CCTCAGGTCC TGCCGGCTAA ACTCTAAGGA TAGGCCATCC	665
35	TCCTGCTGGG TCAGACCTGG AGGCTCACCT GAATTGGAGC CCCTCTGTAC CTATCTGGGC	725
	AACAAAGAAA CCTACCATGA GGCTGGGGCA CAATGAGCTC CCACAACCAC AGCTTTGGTC	785

CACATGATGG TCACACTTGG ATATACCCCA GTGTGGGTAA GGTGGGGTA TTGCAGGGCC 845
 TCCCAACAAT CTCTTTAAAT AAATAAAGGA GTTGTTTCAGG TAAAAAAAAA AAAAAAAAAA 905
 5 AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAA 938

(2) INFORMATION FOR SEQ ID NO:17:

10 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 155 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Gly Thr Val Tyr Phe Val Gln Val Arg Cys Asn Pro Phe Gly Ile Tyr
 20 1 5 10 15
 Gly Ser Lys Lys Ala Gly Ile Trp Ser Glu Trp Ser His Pro Thr Ala
 20 25 30
 Ala Ser Thr Pro Arg Ser Glu Arg Pro Gly Pro Gly Gly Gly Val Cys
 35 40 45
 Glu Pro Arg Gly Gly Glu Pro Ser Ser Gly Pro Val Arg Arg Glu Leu
 50 55 60
 30 Lys Gln Phe Leu Gly Trp Leu Lys Lys His Ala Tyr Cys Ser Asn Leu
 65 70 75 80
 Ser Phe Arg Leu Tyr Asp Gln Trp Arg Ala Trp Met Gln Lys Ser His
 35 85 90 95

Lys Thr Arg Asn Gln Val Gly Lys Leu Gly Glu Ala Cys Val Gly Gly
 100 105 110
 Lys Gly Ala Glu Glu Glu Arg Asp Pro Gly Glu Gln Pro Pro Gln His
 5 115 120 125
 Arg Thr Leu Leu Ser Lys His Arg Thr Arg Gly Ser Cys Pro Arg Ala
 130 135 140
 Asp Gly Val Arg Arg Glu Val Arg Gly Ser Gly
 10 145 150 155

15 (2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 834 base pairs
 (B) TYPE: nucleic acid
 20 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

25

(ix) FEATURE:

(A) NAME/KEY: CDS
 (B) LOCATION: 1..834

30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

CCC ACC CTT CTC ATC GGC TCC TCC CTG CAA GCT ACC TGC TCT ATA CAT 98
 Pro Thr Leu Leu Ile Gly Ser Ser Leu Gln Ala Thr Cys Ser Ile His
 35 51 55 60 65

	GGA GAC ACA CCT GGG GCC ACC GCT GAG GGG CTC TAC TGG ACC CTC AAT	146
	Gly Asp Thr Pro Gly Ala Thr Ala Glu Gly Leu Tyr Trp Thr Leu Asn	
	70 75 80	
5	GGT CGC CGC CTG CCC TCT GAG CTG TCC CGC CTC CTT AAC ACC TCC ACC	194
	Gly Arg Arg Leu Pro Ser Glu Leu Ser Arg Leu Leu Asn Thr Ser Thr	
	85 90 95	
10	CTG GCC CTG GCC CTG GCT AAC CTT AAT GGG TCC AGG CAG CAG TCA GGA	242
	Leu Ala Leu Ala Leu Ala Asn Leu Asn Gly Ser Arg Gln Gln Ser Gly	
	100 105 110	
15	GAC AAT CTG GTG TGT CAC GCC CGA GAC GGC AGC ATT CTG GCT GGC TCC	290
	Asp Asn Leu Val Cys His Ala Arg Asp Gly Ser Ile Leu Ala Gly Ser	
	115 120 125 130	
20	TGC CTC TAT GTT GGC TTG CCC CCT GAG AAG CCC TTT AAC ATC AGC TGC	338
	Cys Leu Tyr Val Gly Leu Pro Pro Glu Lys Pro Phe Asn Ile Ser Cys	
	135 140 145	
25	TGG TCC CGG AAC ATG AAG GAT CTC ACG TGC CGC TGG ACA CCG GGT GCA	386
	Trp Ser Arg Asn Met Lys Asp Leu Thr Cys Arg Trp Thr Pro Gly Ala	
	150 155 200	
30	CAC GGG GAG ACA TTC TTA CAT ACC AAC TAC TCC CTC AAG TAC AAG CTG	434
	His Gly Glu Thr Phe Leu His Thr Asn Tyr Ser Leu Lys Tyr Lys Leu	
	205 210 215	
35	AGG TGG TAC GGT CAG GAT AAC ACA TGT GAG GAG TAC CAC ACT GTG GGG	482
	Arg Trp Tyr Gly Gln Asp Asn Thr Cys Glu Glu Tyr His Thr Val Gly	
	220 225 230	
40	CCC CAC TCA TGC CAT ATC CCC AAG GAC CTG GCC CTC TTC ACT CCC TAT	530
	Pro His Ser Cys His Ile Pro Lys Asp Leu Ala Leu Phe Thr Pro Tyr	
	235 240 245 250	

	GAG ATC TGG GTG GAA GCC ACC AAT CGC CTA GGC TCA GCA AGA TCT GAT	578
	Glu Ile Trp Val Glu Ala Thr Asn Arg Leu Gly Ser Ala Arg Ser Asp	
	255 260 265	
5	GTC CTC ACA CTG GAT GTC CTG GAC GTG GTG ACC ACG GAC CCC CCA CCC	626
	Val Leu Thr Leu Asp Val Leu Asp Val Val Thr Thr Asp Pro Pro Pro	
	270 275 280	
10	GAC GTG CAC GTG AGC CGC GTT GGG GGC CTG GAG GAC CAG CTG AGT GTG	674
	Asp Val His Val Ser Arg Val Gly Gly Leu Glu Asp Gln Leu Ser Val	
	285 290 295	
15	CGC TGG GTC TCA CCA CCA GCT CTC AAG GAT TTC CTC TTC CAA GCC AAG	722
	Arg Trp Val Ser Pro Pro Ala Leu Lys Asp Phe Leu Phe Gln Ala Lys	
	300 305 310	
20	TAC CAG ATC CGC TAC CGC GTG GAG GAC AGC GTG GAC TGG AAG GTG GTG	770
	Tyr Gln Ile Arg Tyr Arg Val Glu Asp Ser Val Asp Trp Lys Val Val	
	315 320 325 330	
	GAT GAC GTC AGC AAC CAG ACC TCC TGC CGT CTC GCG GGC CTG AAG CCC	818
	Asp Asp Val Ser Asn Gln Thr Ser Cys Arg Leu Ala Gly Leu Lys Pro	
	335 340 345	
25	GGC ACC GTT TAC TTC GTC CAA GTG CGT TGT AAC CCA TTC GGG ATC TAT	866
	Gly Thr Val Tyr Phe Val Gln Val Arg Cys Asn Pro Phe Gly Ile Tyr	
	350 355 360	
30	GGG TCG AAA AAG GCG GGA	894
	Gly Ser Lys Lys Ala Gly	
	365	

(2) INFORMATION FOR SEQ ID NO:19:

35

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 278 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Pro Thr Leu Leu Ile Gly Ser Ser Leu Gln Ala Thr Cys Ser Ile His
 10 51 55 60 65

Gly Asp Thr Pro Gly Ala Thr Ala Glu Gly Leu Tyr Trp Thr Leu Asn
 70 75 80

Gly Arg Arg Leu Pro Ser Glu Leu Ser Arg Leu Leu Asn Thr Ser Thr
 85 90 95

Leu Ala Leu Ala Leu Ala Asn Leu Asn Gly Ser Arg Gln Gln Ser Gly
 100 105 110

20 Asp Asn Leu Val Cys His Ala Arg Asp Gly Ser Ile Leu Ala Gly Ser
 115 120 125 130

Cys Leu Tyr Val Gly Leu Pro Pro Glu Lys Pro Phe Asn Ile Ser Cys
 25 135 140 145

Trp Ser Arg Asn Met Lys Asp Leu Thr Cys Arg Trp Thr Pro Gly Ala
 150 155 200

30 His Gly Glu Thr Phe Leu His Thr Asn Tyr Ser Leu Lys Tyr Lys Leu
 205 210 215

Arg Trp Tyr Gly Gln Asp Asn Thr Cys Glu Glu Tyr His Thr Val Gly
 220 225 230

35 Pro His Ser Cys His Ile Pro Lys Asp Leu Ala Leu Phe Thr Pro Tyr
 235 240 245 250

Glu Ile Trp Val Glu Ala Thr Asn Arg Leu Gly Ser Ala Arg Ser Asp
 255 260 265
 Val Leu Thr Leu Asp Val Leu Asp Val Val Thr Thr Asp Pro Pro Pro
 5 270 275 280
 Asp Val His Val Ser Arg Val Gly Gly Leu Glu Asp Gln Leu Ser Val
 285 290 295
 10 Arg Trp Val Ser Pro Pro Ala Leu Lys Asp Phe Leu Phe Gln Ala Lys
 300 305 310
 Tyr Gln Ile Arg Tyr Arg Val Glu Asp Ser Val Asp Trp Lys Val Val
 315 320 325 330
 15 Asp Asp Val Ser Asn Gln Thr Ser Cys Arg Leu Ala Gly Leu Lys Pro
 335 340 345
 Gly Thr Val Tyr Phe Val Gln Val Arg Cys Asn Pro Phe Gly Ile Tyr
 20 350 355 360
 Gly Ser Lys Lys Ala Gly
 365

25

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 143 base pairs
 30 (B) TYPE: nucleic acids
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

35 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

GGCATGAAGG CTTAGGGTGG GGATCGGTAG GACCCATGCA CCCAGAGAAA GGGACTGGTG 60

GCAACTTTCA AACTCTCTGG GGAAGGAAGA AGGGCTGAAA GAGG 104

5 ATG AAC GGG CTC AGA CAC AGC TGT AAT CAG CCC CCA GGA 143

Met Asn Gly Leu Arg His Ser Cys Asn Gln Pro Pro Gly

5

10

10 (2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13 amino acids

(B) TYPE: amino acids

15 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

20

Met Asn Gly Leu Arg His Ser Cys Asn Gln Pro Pro Gly

5

10

25

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

30 (A) LENGTH: 1930 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

35 (ii) MOLECULE TYPE: DNA.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

	GGCACGAGCT TCGCTGTCCG CGCCCAGTGA CGCGCGTGCG GACCCGAGCC CCAATCTGCA	60
5	CCCCGCAGAC TCGCCCCCGC CCCATACCGG CGTTGCAGTC ACCGCCCCTT GCGCGCCACC	120
	CCCAATGCCC GCGGGTCGCC CGGGCCCCGT CGCCCAATCC GCGCGGCGGC CGCCGCGGCC	180
10	GCTGTCTCTG CTGTGGTCGC CTCTGTTGCT CTGTGTCTCT GGGGTGCCTC GGGGCGGATC	240
	GGGAGCCCAC ACAGCTGTAA TCAGCCCCCA GGACCCCACC CTTCTCATCG GCTCCTCCCT	300
	GCAAGCTACC TGCTCTATAC ATGGAGACAC ACCTGGGGCC ACCGCTGAGG GGCTCTACTG	360
15	GACCCCTCAAT GGTCGCCGCC TGCCCTCTGA GCTGTCCCGC CTCCTTAACA CCTCCACCCT	420
	GGCCCTGGCC CTGGCTAACC TTAATGGGTC CAGGCAGCAG TCAGGAGACA ATCTGGTGTG	480
	TCACGCCCCG GACGGCAGCA TTCTGGCTGG CTCCTGCCTC TATGTTGGCT TGCCCCCTGA	540
20	GAAGCCCTTT AACATCAGCT GCTGGTCCCG GAACATGAAG GATCTCACGT GCCGCTGGAC	600
	ACCGGGTGCA CACGGGGAGA CATTCTTACA TACCAACTAC TCCCTCAAGT ACAAGCTGAG	660
25	GTGGTACGGT CAGGATAACA CATGTGAGGA GTACCACACT GTGGGCCCTC ACTCATGCCA	720
	TATCCCCAAG GACCTGGCCC TCTTCACTCC CTATGAGATC TGGGTGGAAG CCACCAATCG	780
	CCTAGGCTCA GCAAGATCTG ATGTCTCAC ACTGGATGTC CTGGACGTGG TGACCACGGA	840
30	CCCCCACC GACGTGCACG TGAGCCGCGT TGGGGGCCTG GAGGACCAGC TGAGTGTGCG	900
	CTGGGTCTCA CCACCAGCTC TCAAGGATTT CCTCTTCCAA GCCAAGTACC AGATCCGCTA	960
35	CCGCGTGGAG GACAGCGTGG ACTGGAAGGT GGTGGATGAC GTCAGCAACC AGACCTCCTG	1020
	CCGTCTCGCG GGCCTGAAGC CCGGCACCGT TTACTTCGTC CAAGTGCGTT GTAACCCATT	1080

CGGGATCTAT GGGTCGAAAA AGGCGGGAAT CTGGAGCGAG TGGAGCCACC CCACCGCTGC 1140
CTCCACCCCT CGAAGTGAGC GCCCGGGCCC GGGCGGCGGG GTGTGCGAGC CGCGGGGCGG 1200
5 CGAGCCCAGC TCGGGCCCCG TGCGGCGCGA GCTCAAGCAG TTCCTCGGCT GGCTCAAGAA 1260
GCACGCATAC TGCTCGAACC TTAGTTTCCG CCTGTACGAC CAGTGGCGTG CTTGGATGCA 1320
GAAGTCACAC AAGACCCGAA ACCAGGTAGG AAAGTTGGGG GAGGCTTGCG TGGGGGGTAA 1380
10 AGGAGCAGAG GAAGAGAGAG ACCCGGGTGA GCAGCCTCCA CAACACCGCA CTCTTCTTTC 1440
CAAGCACAGG ACGAGGGGAT CCTGCCCTCG GGCAGACGGG GTGCGGCGAG AGGTAAGGGG 1500
15 GTCTGGGTGA GTGGGGCCTA CAGCAGTCTA GATGAGGCCC TTTCCCTCC TTCGGTGTG 1560
CTCAAAGGGA TCTCTTAGTG CTCATTTAC CCACTGCAAA GAGCCCCAGG TTTTACTGCA 1620
TCATCAAGTT GCTGAAGGGT CCAGGCTTAA TGTGGCCTCT TTTCTGCCCT CAGGTCCTGC 1680
20 CGGCTAAACT CTAAGGATAG GCCATCCTCC TGCTGGGTCA GACCTGGAGG CTCACCTGAA 1740
TTGGAGCCCC TCTGTACCTA TCTGGGCAAC AAAGAAACCT ACCATGAGGC TGGGGCACAA 1800
25 TGAGCTCCCA CAACCACAGC TTTGGTCCAC ATGATGGTCA CACTTGGATA TACCCAGTG 1860
TGGGTAAGGT TGGGGTATTG CAGGGCCTCC CAACAATCTC TTAAATAAA TAAAGGAGT 1920
GTTCAGGTAA 1930
30

(2) INFORMATION FOR SEQ ID NO:23:

- 35 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 560 base pairs
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

10	TCCAGGCAGC GGTCTGGGGGA CAACCTCGTG TGCCACGCCC GTGACGGCAG CATCCTGGCT	60
	GGCTCCTGCC TCTATGTTGG CCTGCCCCCA GAGAAACCCG TCAACATCAG CTGCTGGTCC	120
	AAGAACATGA AGGACTTGAC CTGCCGCTGG ACGCCAGGGG CCCACGGGGA GACCTTCCTC	180
15	CACACCAACT ACTCCCTCAA GTACAAGCTT AGGTGGTATG GCCAGGACAA CACATGTGAG	240
	GAGTACCACA CAGTGGGGCC CCACTCCTGC CACATCCCCA AGGACCTGGC TCTCTTTACG	300
20	CCCTATGAGA TCTGGGTGGA GGCCACCAAC CGCCTGGGCT CTGCCCCGCTC CGATGTACTC	360
	ACGCTGGATA TCCTGGATGT GGTGACCACG GACCCCCCGC CCGACGTGCA CGTGAGCCGC	420
	GTCGGGGGCC TGGAGGACCA GCTGAGCGTG CGCTGGGTGT CGCCACCCGC CCTCAAGGAT	480
25	TTCCTTTTTC AAGCCAAATA CCAGATCCGC TACCGAGTGG AGGACAGTGT GGAATGGAAG	540
	GTGGTGGACG ATGTGAGCAA	560

30

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1391 base pairs

35

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(ix) FEATURE:

5 (A) NAME/KEY: CDS
(B) LOCATION: 1..1053

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

10 ACC CTC AAC GGG CGC CGC CTG CCC CCT GAG CTC TCC CGT GTA CTC AAC 48
Thr Leu Asn Gly Arg Arg Leu Pro Pro Glu Leu Ser Arg Val Leu Asn
1 5 10 15

15 GCC TCC ACC TTG GCT CTG GCC CTG GCC AAC CTC AAT GGG TCC AGG CAG 96
Ala Ser Thr Leu Ala Leu Ala Leu Ala Asn Leu Asn Gly Ser Arg Gln
20 25 30

20 CGG TCG GGG GAC AAC CTC GTG TGC CAC GCC CGT GAC GGC AGC ATC CTG 144
Arg Ser Gly Asp Asn Leu Val Cys His Ala Arg Asp Gly Ser Ile Leu
35 40 45

25 GCT GGC TCC TGC CTC TAT GTT GGC CTG CCC CCA GAG AAA CCC GTC AAC 192
Ala Gly Ser Cys Leu Tyr Val Gly Leu Pro Pro Glu Lys Pro Val Asn
50 55 60

30 ATC AGC TGC TGG TCC AAG AAC ATG AAG GAC TTG ACC TGC CGC TGG ACG 240
Ile Ser Cys Trp Ser Lys Asn Met Lys Asp Leu Thr Cys Arg Trp Thr
65 70 75 80

CCA GGG GCC CAC GGG GAG ACC TTC CTC CAC ACC AAC TAC TCC CTC AAG 288
Pro Gly Ala His Gly Glu Thr Phe Leu His Thr Asn Tyr Ser Leu Lys
85 90 95

35 TAC AAG CTT AGG TGG TAT GGC CAG GAC AAC ACA TGT GAG GAG TAC CAC 336
Tyr Lys Leu Arg Trp Tyr Gly Gln Asp Asn Thr Cys Glu Glu Tyr His
100 105 110

	ACA GTG GGG CCC CAC TCC TGC CAC ATC CCC AAG GAC CTG GCT CTC TTT	384
	Thr Val Gly Pro His Ser Cys His Ile Pro Lys Asp Leu Ala Leu Phe	
	115 120 125	
5	ACG CCC TAT GAG ATC TGG GTG GAG GCC ACC AAC CGC CTG GGC TCT GCC	432
	Thr Pro Tyr Glu Ile Trp Val Glu Ala Thr Asn Arg Leu Gly Ser Ala	
	130 135 140	
10	CGC TCC GAT GTA CTC ACG CTG GAT ATC CTG GAT GTG GTG ACC ACG GAC	480
	Arg Ser Asp Val Leu Thr Leu Asp Ile Leu Asp Val Val Thr Thr Asp	
	145 150 155 160	
15	CCC CCG CCC GAC GTG CAC GTG AGC CGC GTC GGG GGC CTG GAG GAC CAG	528
	Pro Pro Pro Asp Val His Val Ser Arg Val Gly Gly Leu Glu Asp Gln	
	165 170 175	
20	CTG AGC GTG CGC TGG GTG TCG CCA CCC GCC CTC AAG GAT TTC CTC TTT	576
	Leu Ser Val Arg Trp Val Ser Pro Pro Ala Leu Lys Asp Phe Leu Phe	
	180 185 190	
25	CAA GCC AAA TAC CAG ATC CGC TAC CGA GTG GAG GAC AGT GTG GAC TGG	624
	Gln Ala Lys Tyr Gln Ile Arg Tyr Arg Val Glu Asp Ser Val Asp Trp	
	195 200 205	
30	AAG GTG GTG GAC GAT GTG AGC AAC CAG ACC TCC TGC CGC CTG GCC GGC	672
	Lys Val Val Asp Asp Val Ser Asn Gln Thr Ser Cys Arg Leu Ala Gly	
	210 215 220	
35	CTG AAA CCC GGC ACC GTG TAC TTC GTG CAA GTG CGC TGC AAC CCC TTT	720
	Leu Lys Pro Gly Thr Val Tyr Phe Val Gln Val Arg Cys Asn Pro Phe	
	225 230 235 240	
40	GGC ATC TAT GGC TCC AAG AAA GCC GGG ATC TGG AGT GAG TGG AGC CAC	768
	Gly Ile Tyr Gly Ser Lys Lys Ala Gly Ile Trp Ser Glu Trp Ser His	
	245 250 255	

	CCC ACA GCC GCC TCC ACT CCC CGC AGT GAG CGC CCG GGC CCG GGC GGC	816
	Pro Thr Ala Ala Ser Thr Pro Arg Ser Glu Arg Pro Gly Pro Gly Gly	
	260 265 270	
5	GGG GCG TGC GAA CCG CGG GGC GGA GAG CCG AGC TCG GGG CCG GTG CGG	864
	Gly Ala Cys Glu Pro Arg Gly Gly Glu Pro Ser Ser Gly Pro Val Arg	
	275 280 285	
	CGC GAG CTC AAG CAG TTC CTG GGC TGG CTC AAG AAG CAC GCG TAC TGC	912
0	Arg Glu Leu Lys Gln Phe Leu Gly Trp Leu Lys Lys His Ala Tyr Cys	
	290 295 300	
	TCC AAC CTC AGC TTC CGC CTC TAC GAC CAG TGG CGA GCC TGG ATG CAG	960
	Ser Asn Leu Ser Phe Arg Leu Tyr Asp Gln Trp Arg Ala Trp Met Gln	
5	305 310 315 320	
	AAG TCG CAC AAG ACC CGC AAC CAG CAC AGG ACG AGG GGA TCC TGC CCT	1008
	Lys Ser His Lys Thr Arg Asn Gln His Arg Thr Arg Gly Ser Cys Pro	
	325 330 335	
0	CGG GCA GAC GGG GCA CGG CGA GAG GTC CTG CCA GAT AAG CTG TAGGGGCTCA	1060
	Arg Ala Asp Gly Ala Arg Arg Glu Val Leu Pro Asp Lys Leu	
	340 345 350	
5	GGCCACCCTC CCTGCCACGT GGAGACGCAG AGGCCGAACC CAAACTGGGG CCACCTCTGT	1120
	ACCCTCACTT CAGGGCACCT GAGCCCCTCA GCAGGAGCTG GGGTGGCCCC TGAGCTCCAA	1180
	CGGCCATAAC AGCTCTGACT CCCACGTGAG GCCACCTTTG GGTGCACCCC AGTGGGTGTG	1240
0	TGTGTGTGTG TGAGGGTTGG TTGAGTTGCC TAGAACCCTT GCCAGGGCTG GGGGTGAGAA	1300
	GGGGAGTCAT TACTCCCCAT TACCTAGGGC CCCTCCAAAA GAGTCCTTTT AAATAAATGA	1360
5	GCTATTTAGG TGCAAAAAA AAAAAAAAAA A	1391

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 350 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

Thr Leu Asn Gly Arg Arg Leu Pro Pro Glu Leu Ser Arg Val Leu Asn
 1 5 10 15

15 Ala Ser Thr Leu Ala Leu Ala Leu Ala Asn Leu Asn Gly Ser Arg Gln
 20 25 30

Arg Ser Gly Asp Asn Leu Val Cys His Ala Arg Asp Gly Ser Ile Leu
 35 40 45

20 Ala Gly Ser Cys Leu Tyr Val Gly Leu Pro Pro Glu Lys Pro Val Asn
 50 55 60

Ile Ser Cys Trp Ser Lys Asn Met Lys Asp Leu Thr Cys Arg Trp Thr
 25 65 70 75 80

Pro Gly Ala His Gly Glu Thr Phe Leu His Thr Asn Tyr Ser Leu Lys
 85 90 95

30 Tyr Lys Leu Arg Trp Tyr Gly Gln Asp Asn Thr Cys Glu Glu Tyr His
 100 105 110

Thr Val Gly Pro His Ser Cys His Ile Pro Lys Asp Leu Ala Leu Phe
 115 120 125

35 Thr Pro Tyr Glu Ile Trp Val Glu Ala Thr Asn Arg Leu Gly Ser Ala
 130 135 140

	Arg Ser Asp Val Leu Thr Leu Asp Ile Leu Asp Val Val Thr Thr Asp	
	145	150 155 160
5	Pro Pro Pro Asp Val His Val Ser Arg Val Gly Gly Leu Glu Asp Gln	
	165	170 175
	Leu Ser Val Arg Trp Val Ser Pro Pro Ala Leu Lys Asp Phe Leu Phe	
	180	185 190
10	Gln Ala Lys Tyr Gln Ile Arg Tyr Arg Val Glu Asp Ser Val Asp Trp	
	195	200 205
	Lys Val Val Asp Asp Val Ser Asn Gln Thr Ser Cys Arg Leu Ala Gly	
	210	215 220
15	Leu Lys Pro Gly Thr Val Tyr Phe Val Gln Val Arg Cys Asn Pro Phe	
	225	230 235 240
	Gly Ile Tyr Gly Ser Lys Lys Ala Gly Ile Trp Ser Glu Trp Ser His	
20	245	250 255
	Pro Thr Ala Ala Ser Thr Pro Arg Ser Glu Arg Pro Gly Pro Gly Gly	
	260	265 270
25	Gly Ala Cys Glu Pro Arg Gly Gly Glu Pro Ser Ser Gly Pro Val Arg	
	275	280 285
	Arg Glu Leu Lys Gln Phe Leu Gly Trp Leu Lys Lys His Ala Tyr Cys	
	290	295 300
30	Ser Asn Leu Ser Phe Arg Leu Tyr Asp Gln Trp Arg Ala Trp Met Gln	
	305	310 315 320
	Lys Ser His Lys Thr Arg Asn Gln His Arg Thr Arg Gly Ser Cys Pro	
35	325	330 335

Arg Ala Asp Gly Ala Arg Arg Glu Val Leu Pro Asp Lys Leu
340 345 350

5 (2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

20 TCCAGGCAGC GGTCTGGGGGA CAAC

24

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

30

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

35

TTGCTCACAT CGTCCACCAC CTTC

24

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 6663 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

15 CCCAGAACTC TTGGACGCTG AGGCAGGAGG ATTCCCAAGT TTCAAGACAG TGTGTTTCTA 60
GGTAATGAGA CCCTGTCAAG AAAAGAAAAG AAATAAAGAG ACAAGAAAAT GTTTATAGGC 120
TGTGAGACAG CTTGGTGGGT AAGGGGCACT TGCCTCCAAT CAAGATGACC TCAGCCCCAT 180
20 CCCTAGGAAT CCATGGTAGA AGGAGAAAGC AAACCTCGCAG CTGCTGACCT CCATACATGT 240
GCTCCAATGT GCACACACAC AGGGAGACAT AATCAATTAA TAGGATGTAT TTGCTTAGAT 300
25 TTGAGTAGGC ATTTATGACT GATGTTTTAA AATTTTTATT TGATTTTATG AAAATATAACC 360
TGTTTGTATT TGGTTTGGTT TGGTTTGAGT TTTGTTTATT TGAGACAGGG CTTCTCTGTG 420
TAGTCCTGGC TGTCCTTGGA ACTCACTCTG TAGACCAGGC TGGCCTTGAA CTCAGAAATC 480
30 CGCCTGCTTG TGCTTCCCAA GTGCTTAGAT TAAAGGTGTG CACTGCCATT CAGCAAAATT 540
GCATACTTTA ACCCCAGTAT TTGGGAGGCA GAGGCAGACT AATGTGTGAA TTCCAGGCTA 600
35 GCCAAGGATA CAGAGTGAGA CCCTATTCTT ACCCTCCCCC CCCAAAACCC CAAAATGTAT 660
TTTGTGCTTG TGTATGTACA TGTGTGTTGC AGCACGTAAA TGTCCAAGGA CAACTTGTAG 720

	AAGTTCTCTC CGTTCACAGT CTAAGTCCTG AATTCAAAC T AAGGTCCTCA GGCTTAGCCA	780
	CAGTCTTCTT TATGTACTGA GCCATTTTAC TGGCCCTGGA TTGACTGATG AATTAATTTT	840
5	TGAGATAAGG TCTCTTGTAG CTCTAGCTAG GCTCAAAC TA TGAAC TCCCA AGGTCATCTT	900
	GAGCTGCTGG TACTCTTGCT TCCACCCCAA GTGGTGGAAT GATACTCAGG CAGCACTTCT	960
	CTGGGGAAGG GGCTGGCCTT GGCCTTGATT TTGTTGCCTC AGCTTCAATG AGTGCTTGGG	1020
10	TCTCGTTGTT TCTTTTCTTT ATCTGTGAAA TGGGTGAACA CCTGTTCAAG ACTTCCTGAC	1080
	TCTTGAAACA TCCAGGCAGG GTGAGGGACT TGAAGTGGGC TCATCCCATG CCTAACAAAG	1140
15	TGTCGTCTTT GACCCCAGAC ACAGCTGTAA TCAGCCCCCA GGACCCACC CTTCTCATCG	1200
	GCTCCTCCCT GCAAGCTACC TGCTCTATAC ATGGAGACAC ACCTGGGGCC ACCGCTGAGG	1260
	GGCTCTACTG GACCTTCAAT GGTCGCCGCC TGCCCTCTGA GCTGTCCCGC CTCCTTAACA	1320
20	CCTCCACCCT GGCCCTGGCC CTGGCTAACC TTAATGGGTC CAGGCAGCAG TCAGGAGACA	1380
	ATCTGGTGTG TCACGCCCCG GACGGCAGCA TTCTGGCTGG CTCCTGCCTC TATGTTGGCT	1440
25	GTAAGTGGGG CCCAGACAC TCAGAGATAG ATGGGGGTTG GCAATGACAG ATTTAGAGCC	1500
	TGGGTCTTCT GTCCTGGGGC AGAGCCATGG GCTCTCACTT GCATGCAGGC ATGGTCATAC	1560
	CCAGCACAGG CATTGCAACT CTAGGGACAG CTGTGGCTGC ACTGTCCCCT GTGTACCCCA	1620
30	CAGCTTTAGA AAAGCTGTCA TGTTTTCTTT GTAGTGCCCC CTGAGAAGCC CTTTAACATC	1680
	AGCTGCTGGT CCCGGAACAT GAAGGATCTC ACGTGCCGCT GGACACCGGG TGCACACGGG	1740
35	GAGACATTCT TACATACCAA CTACTCCCTC AAGTACAAGC TGAGGTTGGT ACCCAGCCAA	1800
	GCCTTGCTGT GTGACTTCTG GCAATACTTA CTTTCTCTGA TCAAATATGT TCCTGTTTAT	1860

	GAACTCAAAA GGGACTCTCG CACCTCCACA GGTGGTACGG TCAGGATAAC ACATGTGAGG	1920
	AGTACCACAC TGTGGGCCCT CACTCATGCC ATATCCCCAA GGACCTGGCC CTCTTCACTC	1980
5	CCTATGAGAT CTGGGTGGAA GCCACCAATC GCCTAGGCTC AGCAAGATCT GATGTCCTCA	2040
	CACTGGATGT CCTGGACGTG GGTGAGCCCC CAGTGTCCAC CTGTGTTCTG CCCTAGACCT	2100
	TATAGGGCGC CTCCCCCCCC TCCCCCAGA CTTTTTGTT CTTCTAGAGG TCTTAGCCAC	2160
10	AGCCACGGTG GTTGCAGGAC AGTGGTTGTT CATAACTTAA TGCAAAGACT TTCCCCCAAG	2220
	ACAGTCAAGA TTTTCCCCCT CCCCACCCCC AACACACACA TACACACACA CTCTGCAGAG	2280
15	AACACCTGGC CTGACCACCC TCCCTCTCTA CAGCCCAGGT GTTCAGAAGG GAGTCCTAGG	2340
	GGACTGAGAG GAGGCGCCCA GGTCTGAAGG CGCCCCAGGA AGCCGAGGCC TTGAGCTGGG	2400
	GGGGGGGGCG AGGGTTGGAG GCACGAACTG GATGATCCCT GAGCACAACCT GGGCCTAATC	2460
20	TAATTAGGGT GTTCCCAGCC CAAAGCAGCC TGGGCCATT AACCCTTCAA GTGCCTCACT	2520
	GAAGACTCAG GGGAGAGATC AGCTTGTA CTCTCCATGG TCCCCCAGGA GGGTTCCTGG	2580
25	GTGCCCCCTG CTCATTCCCA CATCCAGAGG TTTGTGTCT TCCTGGCATC TAACCCTCAG	2640
	TTGTGCTCTG TGGCTGGCAC AGCTGCCCCG TGGAGGCTCT TGGTAATGTA CAAGGCATCA	2700
	GAGGTGGACA TGGGATGGGG ATACATAGGG ATGGAGCCAA ATAGCACCTC AAGGTGGGGT	2760
30	GATATACAAT AAAGCTTGTC ACCCTGACGC TCAGAAAGCC TACTCATGAT GATCACAATT	2820
	GTTGACATCA CTCTGGGACA TGTAAGTGA CCCTAGCTCA AAACACAGAC AGTAGCTTTA	2880
35	AGAGTCAGCT TGTGACTTAA TACTGGAAC CAGGGCCTAA TAGGTGCTGG GTGATGCTCG	2940
	CCTCACTCCC TGTTTAGTGA GATCTCTGCG CTAATCTCCA CCCCAGCTGG GTGGGCTGCT	3000

	CTGTCCCCTT GAGGGCAGGA ATGTGTGTCT TCCATCAGAG ATAGGACCCG TGGTAGCAGC	3060
	AACTGCTGCT GGCTGTTTCT GGAATATTAA ATGACAGTAA TCTATCAGGC CTGGGTGAGT	3120
5	AGCTAACAGG GGTGGGGGCG TGGTCTGGAA AACGCAGATA GGGTCATAGG AGCCACTGCA	3180
	GCCTAGATTA CACCACTGGG TGTCTGTCA CTAGGCCATT CTCACCAAGC AGTCCTCAGA	3240
	ACTGGGAGCA CTGTTGCCAG CATTTAATGC CAGCATTTAA TGCCAGCATT AGGGGAGGCA	3300
10	GAGGCAGAAG GATCTCTCTG AGTTCAAGGC CATCCTGAAT TTACATAAAG AGCTCCAGGC	3360
	CAGCCAGGGT GCGCAGTAAA ACCTTGTCTC AAAAAACAAA GCATCTTTAG TGACCAGGCT	3420
15	TGCTCCACCC CCAGTGACCA CGGACCCCCC ACCCGACGTG CACGTGAGCC GCGTTGGGGG	3480
	CCTGGAGGAC CAGCTGAGTG TCGCTGGGT CTCACCACCA GCTCTCAAGG ATTCCTCTT	3540
	CCAAGCCAAG TACCAGATCC GCTACCGCGT GGAGGACAGC GTGGACTGGA AGGTGCCCGT	3600
20	CCCGCCCCGG ACCCGCCCCCT GACCCCGCCC CCCGCATCTG ACTCCTCCCT CACCGTGCAG	3660
	GTGGTGGATG ACGTCAGCAA CCAGACCTCC TGCCGTCTCG CGGGCCTGAA GCCCGGCACC	3720
25	GTTTACTTCG TCCAAGTGCG TTGTAACCCA TTCGGGATCT ATGGGTCGAA AAAGGCGGGA	3780
	ATCTGGAGCG AGTGGAGCCA CCCACCGCT GCCTCCACCC CTCGAAGTGG TGAGCACCTC	3840
	TCCAGGGCTG GCTGGCCCAT GGAATCCCCA ATCCATCCTG TTCCTTCCCC CCCACCCTTT	3900
30	TTTTGAGACA GCGTCTTCAG GTAGCGCATG CTGGCCTTAA ATTCAGTATG TAGTCAAGGA	3960
	TGACCTCGAG CTCCTGGTCT TTTTGTCTCC ACTTAGAGAC AATGGCCAGT GGCCATCACC	4020
35	ACCTTTGGGA GACTAGCCAT GGAGTCTATT TAGCCTGTCA TTTGGTGACA GATGGAGTAC	4080
	AACAGTGTGA CCTCTTGTA GAGAACTGAA GACAGGCTGT TTTTAACCCC AATATCCTAG	4140

GCTCTCTAGA GGTAACTTT ATATAAAATA GAGACTATTA CAGCCAGTTA TCACATGGTC 4200

CCACAGAACC TTTTGTGACA CAACCTATAG ACCACAGTGC CTGTGCCTAC CACATAAGGG 4260

5 TCTCTACTGC TGGCCCACCC CTCCAACCCT TAAAAGGTAA CCTAGGCAGC CTTAATATTT 4320

GCAATCCTCC TACCTCAGCC TCTTGAATGC TCAGAAACCA GGCATTAACC CAAGTTTCTC 4380

10 TTCTCTGGGT CCCTTTCTTA AGGTGGGAGG GCCTAAAGAT GACTTCCTTT GTCTGAAGA 4440

CTCTCCGAGC CCATGGATCT GCACTCTCTA ATATGAAATA TATTGCATAA AATGTCTGGC 4500

CTCAGTTTCC CCACCTGTCA GGTTTAGGCA GCACAGTCGG TCCAAGACAC TTCATTATTT 4560

15 GCAGGCAGTA TAAGAAGAAG CTCCCATCCC CCACCCGCTT CCTCCGGTCC CTAAGACAGA 4620

ATACTTCTAC ACTGAACTG AACTCTCGCA GACGCATATG CTCACTTTAA TGATGATGAA 4680

ATAATGGGGA AACTGAGGCT CCGAGAGATT CCTGGAGGAA GAGGGTCAAA ACCAGCTCCA 4740

20 GGAAGCTCTC CAGCCCCCAT CCGGGCCTCT CCAGGTTCTG GGCTTGGCGG GAGTGAACAC 4800

AGCTGGGAGG GGCTGGAGCC TGGGAGCTTT GGCCCTTGCT CGTGCCACAG ACCTGCGATT 4860

25 CTTGCACGGG AGCCAGCAGG CGGCTGCGTC CGCCCGAGAG ACTGAAGAAG CCGGGGGTAG 4920

GGTTGGAGGG AGGTAAGCAG GGGCTGTGGG GGCCGAAGCT TGTGCCAGGG CCTGTCAGCG 4980

AGTCCCCAGT TTTATTTATG GCGTGAGGCC GATGTCCTTA TCCGCTGGCC TGCTGGGGGA 5040

30 TGGCTGCGGC TGGGGATTGG ACCCAAGGGC TGGCTTCCCA CTCAGTCCTC CAGCCCCTC 5100

CATGTCACAC CCGTGCAATC TCTGAGGCTT ATCTTGGGAA CCGGCCCTTG TTCTGTGCTG 5160

35 TCTGTCTCTA TTTCTGTCAT TCACTTTCCC AGAGCCTTTT TTTTATGCTT TTAATATAAC 5220

TACGTTTTAA AAATTGCTTT TGTATAATGT GTGTGCCTTC GTGAGCGTGC GTGCCACAAC 5280

	ACACACGTGA AGGTTAGAGA ACTTTGTTGA GTAGGCTCCT TCCACCATGT GGGACTAGGG	5340
	CTGGCGACAA GAGCAATTAC TGAGTCATCT CGCCAGCCCC TCACCCCTCA CTTCCCATCC	5400
5	TGTTTGGATA GTCATAGGTA ATCGAAGGTA AATCGCTGGC TTTAATTTCT TAGCTATCCT	5460
	GCCTCAGCCT ACCAAGTGCT GTGCTACCAC GTTTGTGGGA GGGGCTCTCC TCCCAGTGTC	5520
	TGGGGGTGAC ACAGTCCCAA GATCTCTGCT TTCTAGGTCT TTGTCTTAGT TTGCCCCTTG	5580
10	CTTTGTCCGT GTCCCTAGAG TCTCCGGCCC CACTTATCCA TTGACTGGTC TTTCTTTTAC	5640
	CGAATACTCG GTTTTACCTC CCACTGATTT GACTCCCTCC TTTGCTTGTC TCCATCGCCG	5700
15	TGGCATTGCC ATTCCTCTGG GTGACTCTGG GTCCACACCT GACACCTTTC CCAACTTTCC	5760
	CCAGCCGAAG CTGGTCTGGT ATGGGAGGCC GCCGTCCCGC GCGCGCCTCC TGCTGGCCGC	5820
	GCCCCAACAC TGCCGCTCCA TTCTCTTTAG AGCGCCCGGG CCCGGGCGGC GGGGTGTGCG	5880
20	AGCCGCGGGG CGGCGAGCCC AGCTCGGGCC CGGTGCGGCG CGAGCTCAAG CAGTTCCTCG	5940
	GCTGGCTCAA GAAGCACGCA TACTGCTCGA ACCTTAGTTT CCGCCTGTAC GACCAGTGGC	6000
25	GTGCTTGGAT GCAGAAGTCA CACAAGACCC GAAACCAGGT AGGAAAGTTG GGGGAGGCTT	6060
	GCGTGGGGGG TAAAGGAGCA GAGGAAGAGA GAGACCCGGG TGAGCAGCCT CCACAACACC	6120
	GCACTCTTCT TTCCAAGCAC AGGACGAGGG GATCCTGCCC TCGGGCAGAC GGGGTGCGGC	6180
30	GAGAGGTAAG GGGGTCTGGG TGAGTGGGGC CTACAGCAGT CTAGATGAGG CCCTTTCCCC	6240
	TCCTTCGGTG TTGCTCAAAG GGATCTCTTA GTGCTCATTT CACCCACTGC AAAGAGCCCC	6300
35	AGGTTTTACT GCATCATCAA GTTGCTGAAG GGTCCAGGCT TAATGTGGCC TCTTTTCTGC	6360
	CCTCAGGTCC TGCCGGCTAA ACTCTAAGGA TAGGCCATCC TCCTGCTGGG TCAGACCTGG	6420

AGGCTCACCT GAATTGGAGC CCCTCTGTAC CATCTGGGCA ACAAAGAAAC CTACCAGAGG 6480
CTGGGCACAA TGAGCTCCCA CAACCACAGC TTTGGTCCAC ATGATGGTCA CACTTGGATA 6540
5 TACCCCAAGTG TGGGTAGGGT TGGGGTATTG CAGGGCCTCC CAAGAGTCTC TTAAATAAAA 6600
TAAAGGAGTT GTTCAGGTCC CGATGGCCAG TGTGTTTGGG GCCTATGTGC TGGGGTGGGG 6660
GGA 6663

10

(2) INFORMATION FOR SEQ ID NO:29:

15

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 186 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

20

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

25 Asp Pro Thr Leu Leu Ile Gly Ser Ser Leu Gln Ala Thr Cys Ser Ile
1 5 10 15
His Gly Asp Thr Pro Gly Ala Thr Ala Glu Gly Leu Tyr Trp Thr Phe
20 25 30
30 Asn Gly Arg Arg Leu Pro Ser Glu Leu Ser Arg Leu Leu Asn Thr Ser
35 40 45
Thr Leu Ala Leu Ala Leu Ala Asn Leu Asn Gly Ser Arg Gln Gln Ser
35 50 55 60

Gly Asp Asn Leu Val Cys His Ala Arg Asp Gly Ser Ile Leu Ala Gly
 65 70 75 80
 Ser Cys Leu Tyr Val Gly Leu Pro Pro Glu Lys Pro Phe Asn Ile Ser
 5 85 90 95
 Cys Trp Ser Arg Asn Met Lys Asp Leu Thr Cys Arg Trp Thr Pro Gly
 100 105 110
 Ala His Gly Glu Thr Phe Leu His Thr Asn Tyr Ser Leu Lys Tyr Lys
 10 115 120 125
 Leu Arg Leu Val Arg Ser Gly * His Met * Gly Val Pro His Cys
 130 135 140
 15
 Gly Pro Ser Leu Met Pro Tyr Pro Gln Gly Pro Gly Pro Leu His Ser
 145 150 155 160
 Leu * Asp Leu Gly Gly Ser His Gln Ser Pro Arg Leu Ser Lys Ile
 20 165 170 175
 * Cys Pro His Thr Gly Cys Pro Gly Arg
 180 185

25

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 35 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

30

(ii) MOLECULE TYPE: DNA

35

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

AGCTGGCGCG CCTCCCGGGC GGATCGGGAG CCCAC

35

5 (2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 28 base pairs
- (B) TYPE: nucleic acid
- 10 (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

20 AGCTACGCGT TTAGAGTTTA GCCGGCAG

28

(2) INFORMATION FOR SEQ ID NO:32:

25 (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

30

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

35

Met Val Leu Ala Ser Ser Thr Thr Ser Ile His Thr Met Leu Leu Leu
1 5 10 15

Leu Leu Met Leu Phe His Leu Gly Leu Gln Ala Ser Ile Ser
 20 25 30

5

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

10

(ii) MOLECULE TYPE: DNA

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

20

Ile Lys Pro Ser Gly Arg Arg Gly Ala Ala Arg Gly Pro Ala Gly Asp Tyr Lys Asp Asp
 5 10 15 20
 Asp Asp Lys

25

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 73 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

30

(ii) MOLECULE TYPE: DNA

35

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

5 GATCTTGCCC TCGGGCAGAC GGGGTGCGGC GAGAGGTCCT GCCGGCGACT ACAAGGACGA 60
CGATGACAAG TAG 73

10 (2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 73 base pairs
(B) TYPE: nucleic acid
15 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

25 AACGGGAGCC CGTCTGCCCC ACGCCGCTCT CCAGGACGGC CGCTGATGTT CCTGCTGCTA 60
CTGTTTCATCC TAG 73

30

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 27 base pairs
35 (B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

CCCACGCTTC TCATCGGATT CTCCTG

27

10 (2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 27 base pairs

(B) TYPE: nucleic acid

15 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

25

CAGTCCACAC TGTCTCCAC TCGGTAG

27

30 (2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 11832 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

35 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

	GCGGCCGCTG CAGTGATTAC TCACCGCGTG GCGCACCCCA CCCGCGGGCC GCTGAGTGGA	60
5	TTTTTCCGTG GGGGGATGTG AAGAAGTTTA GGGAGAACTC TTCTGCACCG ATGGGAACTA	120
	GGAATGCAGG GTTCGGTCCC GTTCCCCAAA GGACACACCT CTCCCCATAA GCCCACTCAT	180
	AAGGGCTCCC TGCACGCGCT CCGGGACATC CCCATATCCA ATACCCGCAG ATATGATAGT	240
10	TGAGAAGGGA CCAGAGGCCG GAGACTCCCT CCCTGCCTTC TGGCTTTCCC CCCCCCTGC	300
	ACGAAACGAG ACTACAGCGA TGGGAGAGGT GGCATGAAGG CTTAGGGTGG GGATCGGTAG	360
15	GACCCATGCA CCCAGAGAAA GGGACTGGTG GCAACTTTCA AACTCTCTGG GGAAGGAAGA	420
	AGGGCTGAAA GAGGATGAAC GGGCTCAGGT ACTGCTCAAT GTGTGTGTGG CGGACCAAAG	480
	TGGGTATGGG GGCCCCGTAA GAGGGGCGGG GAAGGTGGAT AGGAAGGATC CCGGTAGACT	540
20	GGAGGGGATC CTGGAAAAGC ACCAGGGCTG CGAGCTAGGA ACCCATTCGG AGTTAAGGGT	600
	ACAGGATCCC AGATGAGGGG GTGGGAAGCC TGGGACGGGC GGGACCAGAG AGGGAGGTCC	660
25	CACGGGCTGG TGGGGAAAGA GTGGGGGGCT TCGCGCAGGA GGATGGGACC TTCAGGAGTG	720
	GTAAGTGGGC GGAGGCCGGC CGGGCGGGGC GCGCGGTGCC CGCGGGCGGT GGGAAGGCCG	780
	GTGCGGGGCC CACGATCAAC CCCCCCCCAG GGGCCGGGCC GGGCCGGGGG CGGGGCCGGG	840
30	CGGGGCGAGC GGCGCATTAG CGCCTTGTC AATTTCGGCTG CTCAGACTTG CTCCGGCCTT	900
	CGCTGTCCGC GCCCAGTGAC GCGCGTGAGG ACCCGAGCCC CAATCTGCAC CCCGCAGACT	960
35	CGCCCCCGCC CCATACCGGC GTTGCAGTCA CCGCCCGTTG CGCGCCACCC CCATGCCCCG	1020
	GGGTCGCCCC GGCCCCGTG CCAATCCGC GCGGCGGCCG CCGCGGCCGC TGTCTCGCT	1080

GTGGTCGCCT CTGTTGCTCT GTGTCCTCGG GGTGCCTCGG GGCGGATCGG GAGCCCGTGA 1140

GTACCGTGCG CCCTGCTCCC CACCTCCCCA GGGAAGCCGG GATCCGGCGC CCCGGGGGGT 1200

5 AGTCGCGGGG GATGGAAGAA GGGGCGCGAG CGCCACCTGG ACGTCCCGGG AACAAAGGAA 1260

GGCGGCCCTC GGGGCGCCCT CACCTGTGGG GCTCATGGCA CCACCACCCA GCCTCCCAAG 1320

AGTACCCCGT TATACATCAG AGGCCTCTTA TCTGTATCCC CTTTGCGAGG CTGTCTGGCC 1380

10 AGGCTCAGTT TGAAGGACAT CGCAGTGTCC TGGGACCCCC CTCCTTCAGG GTGCTGGGAC 1440

GCTTCGGGGC GCACGCCTGT GTCTTGATA TCAGAGCGGA AGGGAAGCCT CCCTGGCCGG 1500

15 GGGCGCACGC TTGGGTGCGT TGGGTTGGGT GCTGGCGCAA AGTGGGGTCC CCTCCCCCAT 1560

GAAGTGATGA TCCCCGGGGG GAGGGTGGGG CGTTATCGTG AGCCCTCCTG TCCGCCTGGC 1620

ATGCGGCCCC GCGTCCCTCG GGAATTGCCT CTCCTGTTGG TCGGCGCCGC CCCCTCCCCC 1680

20 CTATAGCAGA CTCCATGCTT TGGTATCCTC GAAGTCCTCT CCACTGGTGG GGCTCACAAC 1740

CGGTCTCATT CAGGCTGCGC TGGGTTGAGA GCCTCTAGCG ACTGAAATTT CGGTGAGGAG 1800

25 CGAGAGCAAG CGTGTCGGG CACCGCGAGC CCAGACTTCA TTGTCTAAGG GGCACCCAGT 1860

GGGGGTCAGC TGCCGAGAGA ATCCCACTGT CCCAGGAGGA ACTCCTGGCC TTGAGCCCCC 1920

ATCACCCAAC GCACACATCC CCGCCAGGAT GCGGTCTCCA CATCCAGACC CTCTCTGGGA 1980

30 CACACCCAAA GACACACAAA AGAGCCCCAC TGGCTTATGT CCCGTCACCC TGCCCTCCGA 2040

CGCGCGCTGC AGCCCAGATG CGTATTCGCA CACCATCGCG GCGCTCGCAT TCCATCCTCT 2100

35 ACACACACAC ACACACACAC ACACACACAC ACACACACAC ACACACAGAC ACGCACACAC 2160

ACACGCACGC ACACACACGC ACGCCCGCAC TCGTGGTCCC ACATTTATTT CACAGGGGAG 2220

GCAACACCGG GGTACGCATA TGGTTGAGTG CACTGGAGAT CTTTCCCCAC CACTCTCAGG 2280

ACCCCATCCG GAGACACAGG CCACACCGCA GGGGCACCAC GCTGCGCTGC TGCTCTGGGC 2340

5 TAGTAGTCTT GTGCAGTTTG TCCGCGGTGT CTGTGGACGC CCTCCCGCTC TTGTCAGSGG 2400

ACAGGAACCT AACTCCTGC TTGCCAAGG CGGCTGGGCA GGTGATGTGG TGACACCCGG 2460

GACCTTTCCG GGGAGTTGGT GTTGCTGCCA AGCCTGGGTA GTTTTTGAAT GCCACCAATA 2520

10 GCGCTAAGCT TTGTTTCCGG GCGGGCTGCA GAGCAACAGG CGAAGGTGGC GGAGTGGGGG 2580

TGGCGCGTGT GTTTTTTCTT TTAAGGGGGA GAGAAATTAA ATAAGAGGTT CTCACACCTC 2640

15 TGCAATCTGT TTGTACTTAC CGTGTGTCTT AACACCTGAC CAGCCAGCCG GTGGGTCGTA 2700

AAAGTGTATG CAGGTACCAG CGGGACAGGA GATGGGGGCC CCTGGGGTAT GGCTGGGATG 2760

GAGGCCACCT TCCCGTTGGC CTTTCAGGGA ATCTCACACT TTTCCCTTTT AAAACACATG 2820

20 GTGTTCTTTT TAATAACGGC AGCAACTCCG CATTGGGAAA GGGGGAAATA AGCTTGTATA 2880

GGCCCCGGCT TTGTGGAAAG GAGGGGAAGA GGGAAGAAAA AAGGAGGGGT GTCTCCTCCA 2940

25 GGCTTAGGGG GCTGTCAGCT GCTGCTCTGT CTAGCTTGGC ATGTGTGTGC CCCAGTCCCC 3000

AGTGGCTTTG GCCCATTGTT TGTGGAAGCC AAGAGGGAGA CTGGAGTCCT CTATCTCTGG 3060

TACTCCAGAG TCAGGCTTCT CAGTCCGAGC CCAGAGAACG TCTTCCCTGT TTTATGGAGG 3120

30 GAATCAGGGA AGGGGGTGCC AGGTGGACTA CGTTCTGCTG AGGACTGTAC CAGTCGCTCG 3180

AAGGAGAAAG CTTGGGCTTG CCCCCCTCCC CCCTCAAGCC ACGAAGGGCA GCTGCTAGGC 3240

35 TAGTGTGGTA AAAGGGCATT ACTCCCCAGC CAGGACCCCC CAGAGAGTCC CCTTCCTGGC 3300

CAGACAAATG CTGGGGAGGG ACAGAGGGGT GTGATCATTG CCCAGGAGTG CAGACAGTGG 3360

	GGTCCCGGGT	CGGGCAGTGC	CTCCCACCCT	GCTGAGGGGG	GCGCCCAGGC	AGGAAGCGGT	3420
	GGGTGGGCCG	GGGTAGAGAC	GCTGGCACGT	CCCAGTTCAT	GCCGAAGGAA	TTCTGAATTA	3480
5	GCGGGCGGCT	GGCTGCCTGG	GACCTCCGGG	GCGGCCCCCT	GGCCCCCGCC	GCTCCGTCTG	3540
	GCCTGCTCCT	CCTGCTCCTT	CGCACGGACG	CTGAGACCTC	CGCTGAGCCC	TGGGACAAGC	3600
	CCCAAATGCA	ACTGCGATTG	CAGGCTTCGC	AAGACCCGCC	TCCTCCCAAG	GCCAAATTTG	3660
10	CCTGGGAGAA	GTCATTCAGG	GCCCAGACTA	GAACCATGTT	GGTGCCACCT	CATCCATCTG	3720
	GGGCATGAAG	GACCGTCCAG	GGCTGCAGTT	TAGCTTCTTA	ATAGGAACCT	GGGGGTGGGT	3780
15	GCAGCCTCTG	TTCTCCGAGC	CTCTTTGGAA	ATCGGTTTTG	TTTTTGTTTT	TGTTTTTTCC	3840
	AATACTCTTT	TCCTCTCATC	CCATCCCGGG	ACTGTTTTTC	TCCCTAAGGG	TTGAGAGCCC	3900
	TGCAGTCTTC	CCTAACCTTT	TCTTTGCTTC	TACCCCAGGG	CCTTTGCACA	TGGAGTCCCA	3960
20	CCTCTCCCCT	TGCCCAACTG	GGGCTCCAGC	CTTACTGCAT	TTGGCTCTTG	GTAAGTGTCC	4020
	CAGGGCCTCT	CTGACACACA	GGGTTGTAGC	CCCAGCTCCC	TCTCTTCTCC	TCCCCCCTTT	4080
25	CTCTTTTGCT	TCTGAGACTT	AATTTTTTTT	TTTTTCTTTT	TGGCTTTTTG	AGACAGGGTT	4140
	TCTCTGTACA	GCCCTGGCTG	CCCTGGCACT	CATTCTGTAG	ACCAGGCTAG	CCTCAAACCT	4200
	ACAAACCTAC	CTGCCTCTGC	CTTTCCAGTG	CTGGCACTAA	AGATGTGGGC	CACCACAACCT	4260
30	AGTAGTTAAG	TGTTTTGCTG	TGTCTTTATT	CCTATAGTGA	CCTCAGTTCC	TGGCATATTG	4320
	TAGGCGATGG	ATGGATGAAT	GGATGGATGG	ATGGATGGAT	GGATGGTTGG	ATGGAGCAAG	4380
35	CTTGAATCGT	CCTGAGTGAA	AAAAGAGACC	TCAGAGAACT	GAATGGAGTT	AGGTTCCCAG	4440
	GGCAGCCTGG	CCTGCTGGTC	TCATGGGAGC	TCCCTGTGAA	ACTTCCCCCA	CACCTCCCAC	4500

	CACCCTGCCA TCCTGTGTGG CTGACAAGAA AGGCCAATGG CCAGATGGGG ACACAGACTC	4560
	AGGGAAGCTT GGAATATGTT CCCCTCCTCA TATCCTAGGC CTTGTTGTCC CCCTGAGGGC	4620
5	CCAGCCTATG AGTAGGGCAG CTGTGGGCTG CCCTAAGGTT GGGTAGGCAA GAAGGGGGTG	4680
	GTCCCTCAGG GTGGGTCACA GGATTGAGGT CATTTCCTAAA GTGGCCATCA CAGTGGCCCT	4740
	AGGAAATGAT TGTGGAGAGT CAGAACTCCT GTTGGGAGTT GTAGAGGGCC TTGCATGTGG	4800
10	GCTTCTGTGG CTGTCCCTTC TCTTGTGGTC CTTTGCACAG TCCCCTCGTG TGTGCTGGGA	4860
	TGTGAGGAGG GCACGGGGAA AATGAAGGCT CAGCCCCCTCA GCTTGCCCTT CACGGTTCAC	4920
15	CCAACAGGGC TCACCTCTCC TCTGGACAGG CTCTCACTGT ATGCACAGAT TGGCCTCACA	4980
	TTTGATTCCC TTCCTTTGGT CTCCTGGGAT GACAAACATT TACCAGGGTA GGATTTTACA	5040
	TTTLAGATAT GTCCATTCTC CAGAAACACA CTTGTGAGGT TAGGGTATCA GTGAAAGGAC	5100
20	ACCACCAGGA CAGACAAAGA ATTGGAGAGG AAGGAAATTG GTAAGCCAGG CCATGCTTGA	5160
	TGGCTTATGT GTAATCCCAG AACTCTGGAC GCTGAGGCAG GAGGATTCCA AGTTTCAAGA	5220
25	CAGTGTGTTT TAGGTAATGA GACCCTGTCA AGAAAAGAAA AGAAATAAAG AGACAAGAAA	5280
	ATGTTTATAG GCTGTGAGAC AGCTTGGTGG GTAAGGGGCA CTTGCCTCCA ATCAAGATGA	5340
	CCTCAGCCCC ATCCCTAGGA ATCCATGGTA GAAGGAGAAA GCAAACCTCCA GCTGCTGACC	5400
30	TCCATACATG TGCTCCAATG TGCACACACA CAGGGAGACA TAATCAATTA ATAGGATGTA	5460
	TTTGCTTAGA TTTGAGTAGG CATTTATGAC TGATGTTTTA AAATTTTTAT TTGATTTTAT	5520
35	GAAAATATAC CTGTTTGTAT TTGGTTTGGT TTGGTTTGAG TTTTGTATAT TTGAGACAGG	5580
	GCTTCTCTGT GTAGTCCTGG CTGTCCTTGG AACTCACTCT GTAGACCAGG CTGGCCTTGA	5640

	ACTCAGAAAT CCGCCTGCTT GTGCTTCCCA AGTGCTTAGA TTAAAGGTGT GCACTGCCAT	5700
	TCAGCAAAAT TGCATACTTT AACCCAGTA TTTGGGAGGC AGAGGCAGAC TAATGTGTGA	5760
5	ATTCCAGGCT AGCCAAGGAT ACAGAGTGAG ACCCTATTCT TACCCTCCCC CCCCCAAACC	5820
	CCAAAATGTA TTTTGTGCTT GTGTATGTAC ATGTGTGTTG CAGCACGTAA ATGTCCAAGG	5880
	ACAACTTGTA GAAGTTCTCT CCGTTCACAG TCTAAGTCCT GAATTCAAAC TAAGGTCCTC	5940
10	AGGCTTAGCC ACAGTCTTCT TTATGTA CTG	6000
	GAATTAATTT TTGAGATAAG GTCTCTTGTA GCTCTAGCTA GGCTCAAAC ATGAACTCCC	6060
15	AAGGTCATCT TGAGCTGCTG GTACTCTTGC TTCCACCCCA AGTGGTGGAA TGATACTCAG	6120
	GCAGCACTTC TCTGGGGAAG GGGCTGGCCT TGGCCTTGAT TTTGTTGCCT CAGCTTCAAT	6180
	GAGTGCTTGG GTCTCGTTGT TTCTTTTCTT TATCTGTGAA ATGGGTGAAC ACCTGTTCAA	6240
20	GACTTCCTGA CTCTTGAAAC ATCCAGGCAG GGTGAGGGAC TTGAAGTGGG CTCATCCCAT	6300
	GCCTAACAAA GTGTCGTCTT TGACCCAGTA CACAGCTGTA ATCAGCCCCC AGGACCCAC	6360
25	CCTTCTCATC GGCTCCTCCC TGCAAGCTAC CTGCTCTATA CATGGAGACA CACCTGGGGC	6420
	CACCGCTGAG GGGCTCTACT GGACCTTCAA TGGTCGCCGC CTGCCCTCTG AGCTGTCCCG	6480
	CCTCCTTAAC ACCTCCACCC TGGCCCTGGC CCTGGCTAAC CTTAATGGGT CCAGGCAGCA	6540
30	GTCAGGAGAC AATCTGGTGT GTCACGCCCG AGACGGCAGC ATTCTGGCTG GCTCCTGCCT	6600
	CTATGTTGGC TGTAAGTGGG GCCCCAGACA CTCAGAGATA GATGGGGGTT GGCAATGACA	6660
35	GATTTAGAGC CTGGGTCTTC TGTCTGGGG CAGAGCCATG GGCTCTCACT TGCATGCAGG	6720
	CATGGTCATA CCCAGCACAG GCATTGCAAC TCTAGGGACA GCTGTGGCTG CACTGTCCCC	6780

5 TGTGTACCCC ACAGCTTTAG AAAAGCTGTC ATGTTTTCTT TGTAGTGCCC CTGAGAAGC 6840

CCTTTAACAT CAGCTGCTGG TCCCGGAACA TGAAGGATCT CACGTGCCGC TGGACACCGG 6900

GTGCACACGG GGAGACATTC TTACATACCA ACTACTCCCT CAAGTACAAG CTGAGGTTGG 6960

TACCCAGCCA AGCCTTGCTG TGTGACTTCT GGCAATACTT ACCTTCTCTG ATCAAATATG 7020

10 TTCCTGTTTA TGAACTCAA AGGGACTCTC GCACCTCCAC AGGTGGTACG GTCAGGATAA 7080

CACATGTGAG GAGTACCACA CTGTGGGCCC TACTCATGC CATATCCCCA AGGACCTGGC 7140

CCTCTTCACT CCCTATGAGA TCTGGGTGGA AGCCACCAAT CGCCTAGGCT CAGCAAGATC 7200

15 TGATGTCCTC AACTGGATG TCCTGGACGT GGGTGAGCCC CCAGTGTTCA CCTGTGTTCT 7260

GCCCTAGACC TTATAGGGCG CCTCCCCCCC ATCCCCCAG ACTTTTGGT TCTTCTAGAG 7320

GTCTTAGCCA CAGCCACGGT GGTTCAGGA CAGTGGTTGT TCATAACTTA ATGCAAAGAC 7380

20 TTTCCCCCAA GACAGTCAAG ATTTTCCCCT CCCCACCCC AACACACACA TACACACACA 7440

CTCTGCAGAG AACACCTGGC CTGACCACCC TCCCTCTCTA CAGCCCAGGT GTTCAGAAGG 7500

25 GAGTCCTAGG GGAAGTGAAG GAGGCGCCCA GGTCTGAAGG CGCCCCAGGA AGCCGAGGCC 7560

TTGAGCTGGG GGGGGGGGCG AGGGTTGGAG GCACGAACTG GATGATCCCT GAGCACAACCT 7620

GGGCCTAATC TAATTAGGGT GTTCCCAGCC CAAAGCAGCC TGGGCCATTT AACCTTCAA 7680

30 GTGCCTCACT GAAGACTCAG GGGAGAGATC AGCTTGACT CTCTCCATGG TCCCCAGGA 7740

GGGTTCCCTG GTGCCCCTGG CTCATTCCCA CATCCAGAGG TTTGTGTCT TCCTGGCATC 7800

35 TAACCCTCAG TTGTGCTCTG TGGCTGGCAC AGCTGCCCCG TGGAGGCTCT TGGTAATGTA 7860

CAAGGCATCA GAGGTGGACA TGGGATGGG ATACATAGG ATGGAGCCAA ATAGCACCTC 7920

	AAGGTGGGGT GATATACAAT AAAGCTTGTC ACCCTGACGC TCAGAAAGCC TACTCATGAT	7980
	GATCACAATT GTTGACATCA CTCTGGGACA TGTAGTGAGA CCCTAGCTCA AAACACAGAC	8040
5	AGTAGCTTTA AGAGTCAGCT TGTGACTTAA TACTGGAAC T CAGGGCCTAA TAGGTGCTGG	8100
	GTGATGCTCG CCTCACTCCC TGTTTAGTGA GATCTCTGCG CTAATCTCCA CCCCAGCTGG	8160
	GTGGGCTGCT CTGTCCCCCTT GAGGGCAGGA ATGTGTGTCT TCCATCAGAG ATAGGACCCG	8220
10	TGGTAGCAGC AACTGCTGCT GGCTGTTTCT GGAATATTAA ATGACAGTAA TCTATCAGGC	8280
	CTGGGTGAGT AGCTAACAGG GGTGGGGGCG TGGTCTGGAA AACGCAGATA GGGTCATAGG	8340
15	AGCCACTGCA GCCTAGATTA CACCACTGGG TGTTCTGTCA CTAGGCCATT CTCACCAAGC	8400
	AGTCCTCAGA ACTGGGAGCA CTGTTGCCAG CATTTAATGC CAGCATTTAA TGCCAGCATT	8460
	AGGGGAGGCA GAGGCAGAAG GATCTCTCTG AGTTCAAGGC CATCCTGAAT TTACATAAAG	8520
20	AGCTCCAGGC CAGCCAGGGT GCGCAGTAAA ACCTTGCTCTC AAAAAACAAA GCATCTTTAG	8580
	TGACCAGGCT TGCTCCACCC CCAGTGACCA CGGACCCCCC ACCCGACGTG CACGTGAGCC	8640
25	GCGTTGGGGG CCTGGAGGAC CAGCTGAGTG TGCGCTGGGT CTCACCACCA GCTCTCAAGG	8700
	ATTTCTCTT CCAAGCCAAG TACCAGATCC GCTACCGCGT GGAGGACAGC GTGGACTGGA	8760
	AGGTGCCCCG CCGCCCCGG ACCCGCCCCCT GACCCCGCCC CCGCATCTG ACTCCTCCCT	8820
30	CACCGTGCAG GTGGTGGATG ACGTCAGCAA CCAGACCTCC TGCCGTCTCG CGGGCCTGAA	8880
	GCCCCGCACC GTTTACTTCG TCCAAGTGCG TTGTAACCCA TTCGGGATCT ATGGGTCGAA	8940
35	AAAGGCGGGA ATCTGGAGCG AGTGGAGCCA CCCCACCGCT GCCTCCACCC CTCGAAGTGG	9000
	TGAGCACCTC TCCAGGGCTG GCTGGCCCAT GGAATCCCCA ATCCATCCTG TTCCTTCCCC	9060

	CCCCACCCCTTT TTTTGAGACA GCGTCTTCAG GTAGCGCATG CTGGCCTTAA ATTCAGTATG	9120
	TAGTCAAGGA TGACCTCGAG CTCCTGGTCT TTTGTCTCC ACTTAGAGAC AATGGCCAGT	9180
5	GGCCATCACC ACCTTTGGGA GACTAGCCAT GGAGTCTATT TAGCCTGTCA TTTGGTGACA	9240
	GATGGAGTAC AACAGTGTGA CCTCTTGTA GAGAACTGAA GACAGGCTGT TTTTAACCCC	9300
	AATATCCTAG GCTCTCTAGA GGTAACTTT ATATAAAATA GAGACTATTA CAGCCAGTTA	9360
10	TCACATGGTC CCACAGAACC TTTTGTGACA CAACCTATAG ACCACAGTGC CTGTGCCTAC	9420
	CACATAAGGG TCTCTACTGC TGGCCCCACCC CTCCAACCCT TAAAAGGTAA CCTAGGCAGC	9480
15	CTTAATATTT GCAATCCTCC TACCTCAGCC TCTTGAATGC TCAGAAACCA GGCATTAACC	9540
	CAAGTTTCTC TTCTCTGGGT CCCTTTCTTA AGGTGGGAGG GCCTAAAGAT GACTTCCTTT	9600
	GTCCTGAAGA CTCTCCGAGC CCATGGATCT GCACTCTCTA ATATGAAATA TATTGCATAA	9660
20	AATGTCTGGC CTCAGTTTCC CCACCTGTCA GGTTTAGGCA GCACAGTCGG TCCAAGACAC	9720
	TTCATTATTT GCAGGCAGTA TAAGAAGAAG CTCCCATCCC CCACCCGCTT CCTCCGGTCC	9780
25	CTAAGACAGA ATACTTCTAC ACTGAACTG AACTCTCGCA GACGCATATG CTCACTTTAA	9840
	TGATGATGAA ATAATGGGGA AACTGAGGCT CCGAGAGATT CCTGGAGGAA GAGGGTCAAA	9900
	ACCAGCTCCA GGAAGCTCTC CAGCCCCCAT CCGGGCCTCT CCAGGTTCTG GGCTTGGCGG	9960
30	GAGTGAACAC AGCTGGGAGG GGCTGGAGCC TGGGAGCTTT GGCCCTTGCT CGTGCCACAGC	10020
	ACCTGCGATT CTGACAGGG AGCCAGCAGG CGGCTGCGTC CGCCGAGAG ACTGAAGAAG	10080
35	CCGGGGGTAG GGTTGGAGGG AGGTAAGCAG GGGCTGTGGG GGCCGAAGCT TGTGCCAGGG	10140
	CCTGTCAGCG AGTCCCCAGT TTTATTTATG GCGTGAGGCC GATGTCCTTA TCCGCTGGCC	10200

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TGCTGGGGGA TGGCTGCGGC TGGGGATTGG ACCCAAGGGC TGGCTTCCCA CTCAGTCCTC 10260
CAGCCCCACTC CATGTCACAC CCGTGCAATC TCTGAGGCTT ATCTTGGGAA CCCGCCCTTG 10320
TTCTGTGCTG TCTGTCTCTA TTTCTGTCAT TCACTTTCCC AGAGCCTTTT TTTTATGCTT 10380
TTAATATAAC TACGTTTTAA AAATTGCTTT TGTATAATGT GTGTGCCTTC GTGAGCGTGC 10440
GTGCCACAAC ACACACGTGA AGGTTAGAGA ACTTTGTTGA GTAGGCTCCT TCCACCATGT 10500
GGGACTAGGG CTGGCGACAA GAGCAATTAC TGAGTCATCT CGCCAGCCCC TCACCCCTCA 10560
CTTCCCATCC TGTTTGGATA GTCATAGGTA ATCGAAGGTA AATCGCTGGC TTTAATTTTCG 10620
TAGCTATCCT GCCTCAGCCT ACCAAGTGCT GTGCTACCAC GTTTGTGGGA GGGGCTCTCC 10680
TCCCAGTGTC TGGGGGTACA CAGTCCCAAG ATCTCTGCTT TCTAGGTCTT TGTCTTAGTT 10740
TGCCCCCTTGC TTTGTCCGTG TCCCTAGAGT CTCCGGCCCC ACTTAGTCTC CATTGATTTC 10800
CTTTCTGACC GAATACTCGG TTTTACCTCC CACTGATTTG ACTCCCTCCT TTGCTTGTCT 10860
CCATCGCCGT GGCATTGCCA TTCCTCTGGG TGA CTCTGGG TCCACACCTG ACACCTTTCC 10920
CAACTTTCCC CAGCCGAAGC TGGTCTGGTA TGGGAGGCCG CCGTCCCCGG CGCGCCTCCT 10980
GCTGGCCCGC CCCCACACT GCCGCTCCAT TCTCTTTAGA GCGCCCGGGC CCGGGCGGGC 11040
GGGTGTGCGA GCCGCGGGG GCGAGCCCA GCTCGGGCCC GGTGCGGCGC GAGCTCAAGC 11100
AGTTCCTCGG CTGGCTCAAG AAGCACGCAT ACTGCTCGAA CCTTAGTTTC CGCCTGTACG 11160
ACCAAGTGGC TGCTTGGATG CAGAAGTCAC ACAAGACCCG AAACCAGGTA GGAAAGTTGG 11220
GGGAGGCTTG CGTGGGGGGT AAAGGAGCAG AGGAAGAGAG AGACCCGGGT GAGCAGCCTC 11280
CACAAACCCG CACTCTTCTT TCCAAGCACA GGACGAGGGG ATCCTGCCCT CGGGCAGACG 11340

GGGTGCGGCG AGAGGTAAGG GGGTCTGGGT GAGTGGGGCC TACAGCAGTC TAGATGAGGC 11400

CCTTTCCCTT CCTTCGGTGT TGCTCAAAGG GATCTCTTAG TGCTCATTTT ACCCACTGCA 11460

5 AAGAGCCCCA GGTTTTACTG CATCATCAAG TTGCTGAAGG GTCCAGGCTT AATGTGGCCT 11520

CTTTTCTGCC CTCAGGTCCT GCCGGCTAAA CTCTAAGGAT AGGCCATCCT CCTGCTGGGT 11580

CAGACCTGGA GGCTCACCTG AATTGGAGCC CCTCTGTACC ATCTGGGCAA CAAAGAAACC 11640

10 TACCAGAGGC TGGGCACAAT GAGCTCCAC AACCACAGCT TTGGTCCACA TGATGGTCAC 11700

ACTTGATAT ACCCCAGTGT GGGTAGGGTT GGGGTATTGC AGGGCCTCCC AAGAGTCTCT 11760

15 TTAAATAAAT AAAGGAGTTG TTCAGGTCCC GATGGCCAGT GTGTTTGGGG CCTATGTGCT 11820

GGGGTGGGGG GA 11832

20 (2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 26 amino acids
- (B) TYPE: amino acids
- 25 (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Protein

30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

35 Val Ile Ser Pro Gln Asp Pro Thr Leu Leu Ile Gly Ser Ser Leu Gln Ala Thr Cys Ser

5 10 15 20

Ile His Gly Asp Thr Pro

25

CLAIMS:

1. A nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding a novel haemopoietin receptor or derivative thereof having the motif:

Trp Ser Xaa Trp Ser [SEQ ID NO:1],

wherein Xaa is any amino acid.

2. A nucleic acid molecule according to claim 1 wherein Xaa is Asp or Glu.

3. A nucleic acid molecule according to claim 1 or 2 wherein said nucleic acid molecule is capable of hybridisation under low stringency conditions at 42°C to:

5N (A/G)CTCCA(A/G)TC(A/G)CTCCA 3N [SEQ ID NO:7]; and

5N (A/G)CTCCA(C/T)TC(A/G)CTCCA 3N [SEQ ID NO:8].

4. A nucleic acid molecule according to claim 3 comprising a sequence of nucleotides substantially as set forth in SEQ ID NO:12 or a nucleotide sequence having at least 60% similarity to the nucleotide sequence set forth in SEQ ID NO:12 or a nucleotide sequence capable of hybridising thereto under low stringency conditions at 42°C.

5. A nucleic acid molecule according to claim 3 comprising a sequence of nucleotides substantially as set forth in SEQ ID NO:14 or a nucleotide sequence having at least 60% similarity to the nucleotide sequence set forth in SEQ ID NO:14 or a nucleotide sequence capable of hybridising thereto under low stringency conditions at 42°C.

6. A nucleic acid molecule according to claim 3 comprising a sequence of nucleotides substantially as set forth in SEQ ID

NO:16 or a nucleotide sequence having at least 60% similarity to the nucleotide sequence set forth in SEQ ID NO:16 or a nucleotide sequence capable of hybridising thereto under low stringency conditions at 42°C.

5

7. A nucleic acid molecule according to claim 3 comprising a sequence of nucleotides substantially as set forth in SEQ ID NO:18 or 24 or a nucleotide sequence having at least 60% similarity to the nucleotide sequence set forth in SEQ ID NO:18 or 24 or a nucleotide sequence capable of hybridising thereto under low stringency conditions at 42°C.

10

8. A nucleic acid molecule according to claim 3 comprising a sequence of nucleotides substantially as set forth in SEQ ID NO:28 or a nucleotide sequence having at least 60% similarity to the nucleotide sequence set forth in SEQ ID NO:28 or a nucleotide sequence capable of hybridising thereto under low stringency conditions at 42°C.

15

9. A nucleic acid molecule according to claim 3 comprising a sequence of nucleotides substantially as set forth in SEQ ID NO:38 or a nucleotide sequence having at least 60% similarity to the nucleotide sequence set forth in SEQ ID NO:38 or a nucleotide sequence capable of hybridising thereto under low stringency conditions at 42°C.

20

25

10. A nucleic acid molecule according to claim 4 or 5 or 6 or 7 or 8 or 9 wherein said haemopoietin receptor is of murine origin.

30

11. A nucleic acid molecule according to claim 9 wherein said haemopoietin receptor is of human origin.

35

12. An expression vector comprising a nucleic acid molecule selected from the list consisting of:

- (i) a nucleotide sequence as set forth in SEQ ID NO:12;
- (ii) a nucleotide sequence as set forth in SEQ ID NO:14;

- (iii) a nucleotide sequence as set forth in SEQ ID NO:16;
(iv) a nucleotide sequence as set forth in SEQ ID NO:18;
(v) a nucleotide sequence as set forth in SEQ ID NO:24;
(vi) a nucleotide sequence as set forth in SEQ ID NO:28; and
5 (vii) a nucleotide sequence as set forth in SEQ ID NO:38.

13. A method for cloning a nucleotide sequence encoding a haemopoietin receptor having the characteristics of NR6 or a derivative thereof, said method comprising searching a
10 nucleotide database for a sequence which encodes an amino acid sequence as set forth in one or more of SEQ ID NO:1, SEQ ID NO:7 and/or SEQ ID NO:8, designing one or more oligonucleotide primers based on the nucleotide sequence located in said search, screening a nucleic acid library with said one or more
15 oligonucleotides and obtaining a clone therefore which encodes NR6 or a part or derivative thereof.

14. An isolated nucleic acid molecule comprising a sequence of nucleotides encoding a haemopoietin receptor or derivative
20 thereof having an amino acid sequence substantially as set forth in SEQ ID NO:13 or having at least about 50% similarity thereto.

15. An isolated nucleic acid molecule comprising a sequence of nucleotides encoding a haemopoietin receptor or derivative
25 thereof having an amino acid sequence substantially as set forth in SEQ ID NO:15 or having at least about 50% similarity thereto.

30 16. An isolated nucleic acid molecule comprising a sequence of nucleotides encoding a haemopoietin receptor or derivative thereof having an amino acid sequence substantially as set forth in SEQ ID NO:17 or having at least about 50% similarity thereto.

35 17. An isolated nucleic acid molecule comprising a sequence of nucleotides encoding a haemopoietin receptor or derivative

thereof having an amino acid sequence substantially as set forth in SEQ ID NO:19 or having at least about 50% similarity thereto.

- 5 18. An isolated nucleic acid molecule comprising a sequence of nucleotides encoding a haemopoietin receptor or derivative thereof having an amino acid sequence substantially as set forth in SEQ ID NO:25 or having at least about 50% similarity thereto.

10

19. An isolated nucleic acid molecule comprising a sequence of nucleotides encoding a haemopoietin receptor or derivative thereof having an amino acid sequence substantially as set forth in SEQ ID NO:29 or having at least about 50% similarity thereto.

15

20. An isolated novel haemopoietin receptor comprising the amino acid motif:

20

Trp Ser Xaa Trp Ser [SEQ ID NO:1]

wherein Xaa is any amino acid.

21. An isolated haemopoietin receptor according to claim 20 wherein Xaa is Asp or Glu.

25

22. An isolated haemopoietin receptor according to claim 21 comprising the amino acid sequence substantially as set forth in SEQ ID NO:13.

30

23. An isolated haemopoietin receptor according to claim 21 comprising the amino acid sequence substantially as set forth in SEQ ID NO:15.

35

24. An isolated haemopoietin receptor according to claim 21 comprising the amino acid sequence substantially as set forth in SEQ ID NO:17.

25. An isolated haemopoietin receptor according to claim 21 comprising the amino acid sequence substantially as set forth in SEQ ID NO:19.

5 26. An isolated haemopoietin receptor according to claim 21 comprising the amino acid sequence substantially as set forth in SEQ ID NO:25.

10 27. An isolated haemopoietin receptor according to claim 21 comprising the amino acid sequence substantially as set forth in SEQ ID NO:29.

15 28. A method for modulating expression of NR6 in a mammal, said method comprising contacting a genetic sequence encoding said NR6 with an effective amount of a modulator of NR6 expression for a time and under conditions sufficient to up-regulate or down-regulate or otherwise modulate expression of NR6, wherein the genetic sequence encoding said NR6 is selected from the nucleotide sequence set forth in SEQ ID NO:12 or 14 or 20 16 or 18 or 24 or 28 or 38 or is a sequence having at least about 60% similarity to at least one of SEQ ID NO:12 or 14 or 16 or 18 or 24 or 28 or 38 and is capable of hybridising thereto under low stringency conditions at 42°C.

25 29. A method of modulating activity of NR6 in a mammal, said method comprising administering to said mammal, a modulating effective amount of a molecule for a time and under conditions sufficient to increase or decrease NR6 activity wherein said NR6 comprises an amino acid sequence:

30

- (i) encoded by a nucleotide sequence selected from the nucleotide sequence set forth in SEQ ID NO:12 or 14 or 16 or 18 or 24 or 28 or 38 or a nucleotide sequence having at least 60% similarity to the nucleotide sequence set forth in SEQ ID NO:12 or 14 or 16 or 18 or 24 or 28 or 38 and which is capable of hybridising thereto under low stringency conditions at 42°C; and

35

(ii) substantially as set forth in SEQ ID NO:12 or 14 or 16 or 18 or 32 or 30 or a sequence having at least 50% similarity thereto.

5 30. A pharmaceutical composition comprising an NR6 receptor in soluble form and one or more pharmaceutically acceptable carriers and/or diluents wherein said NR6 comprises the amino acid sequence:

10 (i) encoded by a nucleotide sequence selected from the nucleotide sequence set forth in SEQ ID NO:12 or 14 or 16 or 18 or 24 or 28 or 38 or a nucleotide sequence having at least 60% similarity to the nucleotide sequence set forth in SEQ ID NO:12 or 14 or 16 or 18 or 24 or 28 or 38
15 and which is capable of hybridising thereto under low stringency conditions at 42°C; and
(ii) substantially as set forth in SEQ ID NO:12 or 14 or 16 or 18 or 32 or 30 or a sequence having at least 50% similarity thereto.

20

31. An isolated antibody or a preparation of antibodies to an NR6 receptor, said NR6 receptor comprising the amino acid sequence:

25 (i) encoded by a nucleotide sequence selected from the nucleotide sequence set forth in SEQ ID NO:12 or 14 or 16 or 18 or 24 or 28 or 38 or a nucleotide sequence having at least 60% similarity to the nucleotide sequence set forth in SEQ ID NO:12 or 14 or 16 or 18 or 24 or 28 or 38
30 and which is capable of hybridising thereto under low stringency conditions at 42°C; and
(ii) substantially as set forth in SEQ ID NO:12 or 14 or 16 or 18 or 24 or 28 or 38 or a sequence having at least 50% similarity thereto.

35

32. A transgenic animal comprising a mutation in at least one allele of the gene encoding NR6.

33. A transgenic animal according to claim 33 comprising a mutation in two alleles of the gene encoding NR6.

5 34. A transgenic animal according to claim 33 or 34 wherein said animal is a murine animal.

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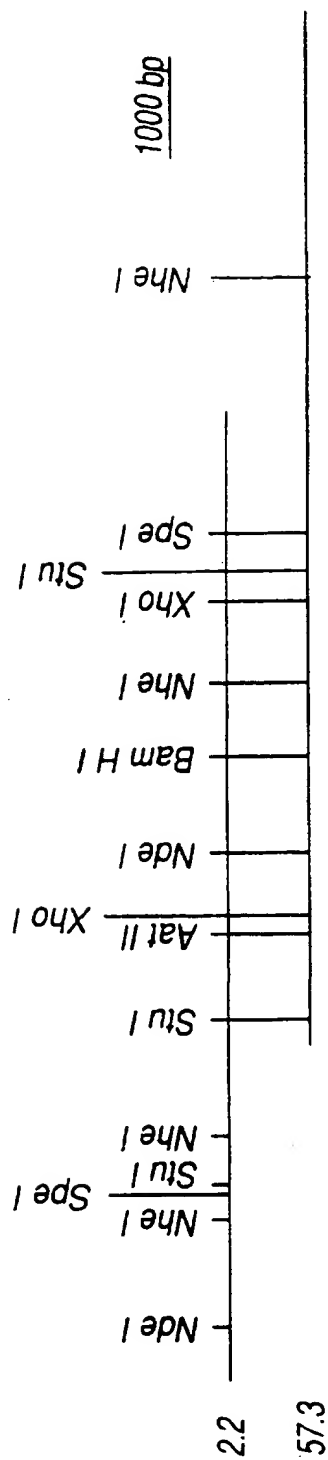
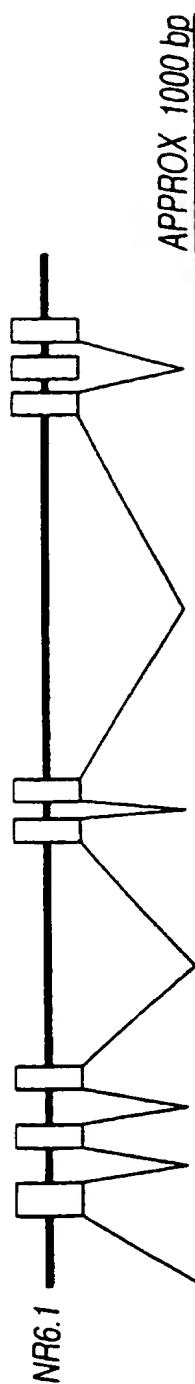


Fig. 1A



APPROX 1000 bp

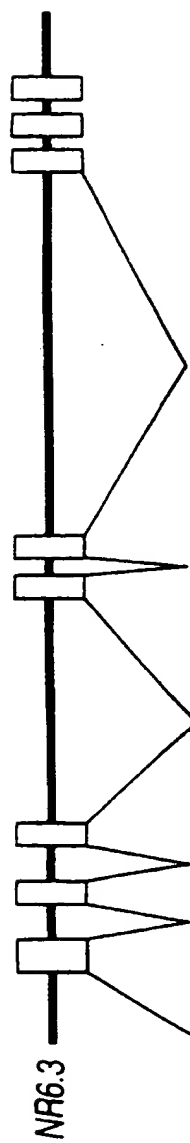
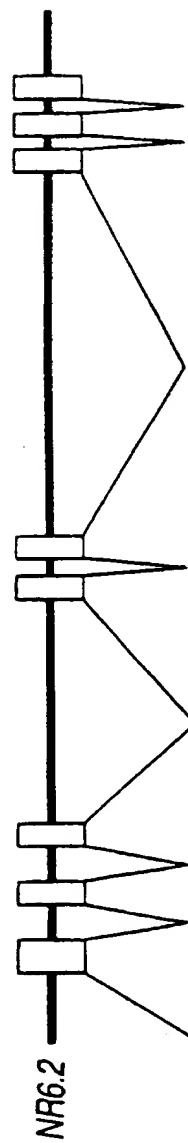


Fig. 1B

$2/43$

$3/43$	$4/43$
$5/43$	$6/43$
$7/43$	$8/43$
$9/43$	$10/43$
$11/43$	$12/43$
$13/43$	$14/43$
$15/43$	$16/43$
$17/43$	$18/43$

Fig.2

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g1	cccagaactct
g38	agttttcaagacagtgtgtt
g83	aagaaaagaaataaagaga
g128	cagcttggtgggtaagggg
g173	agcccccattccctaggaatc
g218	cagctgctgacctccatac
g263	ggagacataatcaattaat
g308	ggcattttatgactgatgtt
g353	aataataacctgtttgtattt
g398	atttgagacagggcttctc
g443	tcactctgtagaccaggct
g488	ttgtgcttcccaagtgtt
g533	gcaaaattgcatactttaa
g578	actaatgtgtgaattccag
g623	ctattcttaccctcccccc
g668	ttgtgtatgtacatgtgtg
g713	acttgtagaagttctctcc
g758	actaagggtcctcaggctta
g803	catttcactggccctggat
g848	aggctctcttgtagctctag
g893	gtcatcttgagctgctggg
g938	aatgatactcaggcagcac
g983	ccttgatttttgttgccctca
g1028	gtttctttttcttttatctgt
g1073	ttcctgactcttgaaacat

Fig.2(i)

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tggacgctgagggcaggaggattccca
tctagggtaatgagaccctgtcaagaa
caagaaaatgttttataggctgtgaga
cacttgcctccaatcaagatgacctc
catggtagaaggagaaagcaaactcg
atgtgctccaatgtgcacacacacag
aggatgtatttgcttagatttgagta
ttaaaattttttatttgattttatgaa
ggttttggttttggttttgagttttgttt
tgtgtagtcctggctgtccttgggaac
ggccttgaactcagaaatccgcctgc
agattaaagggtgtgcactgccattca
ccccagtatttggggagggcagaggcag
gctagccaaggatacagagtgagacc
ccaaaacccccaaaatgtattttgtgc
ttgcagcacgtaaatgtccaaggaca
gttcacagtctaagtcctgaattcaa
gccacagtcttcttttatgtactgagc
tgactgatgaattaatttttgagata
ctaggctcaaactatgaactcccaag
actcttgcttccaccccaagtgggtgg
ttctctgggggaaggggctggccttgg
gcttcaatgagtgcttgggtctcgtt
gaaatgggtgaacacctgttcaagac
ccagggcagggtgagggacttgaagtg

Fig.2(ii)

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g1118	ggctcatcccatgcctaac
g1163	agctgtaatcagccccag
g1208	<u>L Q A T C S</u> <u>CCTGCAAGCTACCTGCTCT</u>
g1253	<u>A E G L Y W</u> <u>CGCTGAGGGGCTCTACTGG</u>
g1298	<u>E L S R L L</u> <u>TGAGCTGTCCCGCCTCCTT</u>
g1343	<u>A N L N G S</u> <u>GGCTAACCTTAATGGGTCC</u>
g1388	<u>C H A R D G</u> <u>GTGTCACGCCCGAGACGGC</u>
g1433	<u>V G</u> <u>TGTTGGCT</u> gtaagtgggggc
g1478	ttggcaatgacagatttag
g1523	agccatgggctctcacttg
g1568	aggcattgcaactctaggg
g1613	gtaccccacagctttagaa

Fig.2(iii)

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aaagtgtcgtcttttgaccccagacac
 D P T L L I G S S
GACCCCAACCCTTCTCATCGGCTCCTC

I H G D T P G A T
ATACATGGAGACACACCTGGGGCCAC

T F N G R R L P S
ACCTTCAATGGTCGCCGCTGCCCTC

N T S T L A L A L
AACACCTCCACCCTGGCCCTGGCCCT

R Q Q S G D N L V
AGGCAGCAGTCAGGAGACAATCTGGT

S I L A G S C L Y
AGCATTCTGGCTGGCTCCTGCCTCTA

cccagacactcagagatagatggggg

agcctgggtcttctgtcctgggggcag
 catgcaggcatgggtcatacccgagcac
 acagctgtggctgcactgtcccctgt

L
 aagctgtcatgttttccttgtagTGC

Fig.2(iv)

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g1658	P P E K P F N <u>CCCCTGAGAAGCCCTTTAA</u>
g1703	K D L T C R W <u>AGGATCTCACGTGCCGCTG</u>
g1748	F L H T N Y S <u>TCTTACATAACCAACTACTC</u>
g1793	ccagccaagccttgctgtg
g1838	tgatcaaatatgttcctgt
g1883	W Y G cctccacag <u>GTGGTACGGT</u>
g1928	T V G P H S <u>CACTGTGGGCCCTCACTCA</u>
g1973	F T P Y E I <u>CTTCACTCCCTATGAGATC</u>
g2018	S A R S D V <u>CTCAGCAAGATCTGATGTC</u>
g2063	tgagccccccagtggtccacc
g2108	cgcctcccccccatcccc
g2153	ttagccacagccacggtgg
g2198	taatgcaaagactttcccc

Fig.2(v)

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I	S	C	W	S	R	N	M
<u>CATCAGCTGCTGGTCCCGGAACATGA</u>							
T	P	G	A	H	G	E	T
<u>GACACCGGGTGCACACGGGGGAGACAT</u>							
L	K	Y	K	L	R		
<u>CCTCAAGTACAAGCTGAG</u> gtttggtac							
tgacttctggcaatacttaccttctc							
ttatgaactcaaaagggaactctcgca							
Q	D	N	T	C	E	E	Y
<u>CAGGATAACACATGTGAGGAGTACCA</u>							
C	H	I	P	K	D	L	A
<u>TGCCATATCCCCAAGGACCTGGCCCT</u>							
W	V	E	A	T	N	R	L
<u>TGGGTGGAAGCCACCAATCGCCTAGG</u>							
L	T	L	D	V	L	D	V
<u>CTCACACTGGATGTCCTGGACGTGG</u> g							
tgtgttctgccctagaccttataggg							
cagacttttttggttcttctagaggtc							
ttgcaggacagtgggttggttcataact							
caagacagtcaagatttttcccctcc							

Fig.2(vi)

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g2243	ccaccccccaacacacacat
g2288	ggcctgaccaccctccctc
g2333	gtcctaggggactgagagg
g2378	ggaagccgaggccttgagc
g2423	acgaactggatgatccctg
g2468	ggtgttcccagcccaaagc
g2513	gcctcactgaagactcagg
g2558	tggtccccccaggagggttc
g2603	tccagagggttttgtgtctt
g2648	ctgtggctggcacagctgc
g2693	aggcatcagagggtggacat
g2738	caaatagcacctcaagggtg
g2783	cctgacgctcagaaagcct
g2828	tcactctgggacatgtagt
g2873	tagctttaagagtcagctt
g2918	taatagggtgctgggtgatg
g2963	tctctgcgctaatactccac
g3008	cttgaggggcaggaatgtgt
g3053	gtagcagcaactgctgctg
g3098	taatctatcaggcctgggt
g3143	gtctggaaaacgcagatag
g3188	ttacaccactgggtgttct
g3233	tcctcagaactgggagcac
g3278	taatgccagcattagggga
g3323	ttcaaggccatcctgaatt
g3368	ggtgcgcgagtaaaaccttg

Fig.2(vii)

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acacacacactctgcagagaacacct
tctacagcccagggtgttcagaaggga
aggcgcccagggtctgaaggcgcccca
tggggggggggggcgagggttggaggc
agcacaactgggcctaataatttag
agcctggggccatttaacccttcaagt
ggagagatcagcttgtactctctcca
ctgggtgccccctggctcattcccaca
cctggcatctaaccctcagttgtgct
cccgtggaggctcttggtaatgtaca
gggatggggatacatagggatggagc
gggtgatatacaataaagcttgtcac
actcatgatgatcacaattgttgaca
gagaccctagctcaaaaacacagacag
gtgacttaataactggaactcagggcc
ctcgccctcactccctgttttagtgaga
cccagctgggtgggctgctctgtccc
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gctgtttctggaataattaaatgacag
gagtagctaacaggggtggggggcgtg
ggtcataggagccactgcagcctaga
gtcactaggccatttctcaccaagcag
tgttgccagcatttaatgccagcatt
ggcagaggcagaaggatctctctgag
tacataaagagctccaggccagccag
tctcaaaaaacaaagcatcttttagtg

Fig.2(viii)

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g3413	accaggcttgctccacccc
g3458	V H V S R V G GTGCACGTGAGCCGCGTTG
g3503	R W V S P P CGCTGGGTCTCACCACCAG
g3548	K Y Q I R Y <u>AAGTACCAGATCCGCTACC</u>
g3593	gtgcccgtcccgcgcccgga
g3638	ctgactcctccctcaccgt
g3683	Q T S C R L A <u>AGACCTCCTGCCGTCTCGC</u>
g3728	F V Q V R C N <u>TCGTCCAAGTGCGTTGTAA</u>
g3773	K A G I W S E <u>AGGCGGGAATCTGGAGCGA</u>
g3818	T P R S <u>CCCCTCGAAGTG</u> gtgagca
g3863	aatccccaatccatcctgt

Fig.2(ix)

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V T T D P P P D
cagTGACCACGGACCCCCCACC CGAC

G L E D Q L S V
GGGGCCTGGAGGACAGCTGAGTGTg

A L K D F L F Q A
CTCTCAAGGATTTCTCTTCCAAGCC

R V E D S V D W K
GCGTGGAGGACAGCGTGGACTGGAAG
cccgcccctgaccccgcccccccgcat

V V D D V S N
gcagGTGGTGGATGACGTCAGCAACC

G L K P G T V Y
GGGCCTGAAGCCCGGCACCGTTTACT

P F G I Y G S K
CCCATTCGGGATCTATGGGTCGAAAA

W S H P T A A S
GTGGAGCCACCCACCGCTGCCTCCA

cctctccagggctggctggcccatgg
tccttccccccccaccctttttttgag

Fig.2(x)

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g3908	acagcgtcttcaggtagcg
g3953	gtcaaggatgacctcgagc
g3998	gacaatggccagtggccat
g4043	agtctatttagcctgtcat
g4088	tgacctcttgtaagagAAC
g4133	tatcctagggtctcttagag
g4178	ttacagccagttatcacat
g4223	acctatagaccacagtgcc
g4268	tgctggccccacccctccaa
g4313	taatatatttgcaatcctcct
g4358	ccaggcatataacccaagtt
g4403	gtggggaggggcctaaagatg
g4448	agcccatggatctgcactc
g4493	tgtctggcctcagtttccc
g4538	cgggtccaagacacttcatt
g4583	cccatccccccacccgcttc
g4628	tacactgaaactgaactct
g4673	atgatgaaataaatgggggaa
g4718	gaagaggggtcaaaaccagc
g4763	gggcctctccagggttctgg
g4808	aggggctggagcctgggag
g4853	ctgcgattcttgcacggga
g4898	gagactgaagaagccgggg
g4943	gctgtggggggccgaagctt
g4988	agttttatttatggcgtga
g5033	ctggggggatggctgcggct

Fig.2(xi)

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catgctggccttaaattcagtatgta
tcctgggtcttttttgtctccacttaga
caccacctttgggagactagccatgg
ttgggtgacagatggagtacaacagtg
tgaagacaggctgtttttaaccccaa
gttaactttatataaaatagagacta
ggtcccacagaaccttttgtcacaca
tgtgcctaccacataagggtctctac
cccttaaaaggtaacctagggcagcct
acctcagcctcttgaatgctcagaaa
tctcttctctgggtccctttcttaag
acttcctttgtcctgaagactctccg
tctaatatgaaatatattgcataaaa
cacctgtcagggttagggcagcacagt
atttgcaggcagtataagaagaagct
ctccgggtccctaagacagaatacttc
cgcagacgcataatgctcactttaatg
actgagggtccgagagattcctggag
tccaggaagctctccagcccccatcc
gcttggcgaggagtgaacacagctggg
ctttggcccttgctcgtgcccagcac
gccagcaggcggtgcgtccgcccga
gtaggggttgaggagggttaagcaggg
gtgccagggcctgtcagcgagtcccc
ggccgatgtccttatccgctggcctg
ggggattggaccaagggtggttc

Fig.2(xii)

SUBSTITUTE SHEET (RULE 26)

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g5078	ccactcagtcctccagccc
g5123	tgaggcttatcttgggaac
g5168	ctatttctgtcattcactt
g5213	aatataactacgtttttaa
g5258	ttcgtgagcgtgcggtgcca
g5303	tttggtgagtaggctcctt
g5348	caagagcaattactgagtc
g5393	tcccatcctgtttggatag
g5438	ggctttaatttcgtagcta
g5483	gctaccacgtttgtgggag
g5528	gacacagtcccaagatctc
g5573	gcccccttgctttgtccgtgt
g5618	cattgactgggtctttcctt
g5663	ctgatttgactccctcctt
g5708	ccattcctctgggtgactc
g5753	actttccccagccgaagct
g5798	gcgcgcgcctcctgctggc
g5843	<div>E R P G</div> tcttttagAGCGCCCGGGCC
g5888	<div>G G E P S S</div> GGCGGCGAGCCCAGCTCGG
g5933	<div>F L G W L K</div> TTCCTCGGCTGGCTCAAGA
g5978	<div>F R L Y D Q</div> TTCCGCCTGTACGACCAGT

Fig.2(xiii)

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actccatgtcacacccggtgcattctc
 ccgcccttggttctgtgctgtctgtct
 tcccagagccttttttttatgctttt
 aattgcttttgtataatgtgtgtgcc
 caacacacacgtgaagggttagagaac
 ccaccatgtgggactagggtggtgga
 atctcgccagcccctcaccctcact
 tcataggtaatcgaaggtaaatcgct
 tcctgcctcagcctaccaagtgtgt
 gggctctcctcccagtggtctgggggt
 tgctttctagggtctttgtcttagttt
 ccctagagtctccggccccacttatc
 taccgaatactcgggttttacctcca
 tgcttgtctccatcgccgtggcattg
 tgggtccacacctgacacctttcca
 ggtctggtatgggaggccgctccc
 cgcgccccaacactgccgctccattc

P G G G V C E P R
CGGGCGGCGGGGTGTGCGAGCCGCGG

G P V R R E L K Q
GCCCGGTGCGGCGCGAGCTCAAGCAG
 K H A Y C S N L S
AGCACGCATACTGCTCGAACCTTAGT

W R A W M Q K S H
GGCGTGCTTGGATGCAGAAGTCACAC

Fig.2(xiv)

SUBSTITUTE SHEET (RULE 26)

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	K T R N Q V
g6023	<u>AAGACCCGAAACCAGGTAG</u>
	G K G A E E
g6068	<u>GGTAAAGGAGCAGAGGAAG</u>
	Q H R T L L
g6113	<u>CAACACCGCACTCTTCTTT</u>
	P R A D G V
	P S G R R G A
g6158	<u>CCTCGGGCAGACGGGGGTGC</u>
g6203	<u>GTGGGGCCTACAGCAGTCT</u>
g6248	TGTTGCTCAAAGGGATCTC
g6293	GAGCCCCAGGTTTTACTGC
g6338	CTTAATGTGGCCTCTTTTC
	*
g6383	<u>CTAAGGATAGGCCATCCTC</u>
g6428	CTGAATTGGAGCCCCCTCTG
g6473	CCAGAGGCTGGGCACAATG
g6518	ACATGATGGTCACACTTGG
g6563	GGTATTGCAGGGCCTCCCA
g6608	TTGTTcAGGTccccgatggc
g6653	ggtagggggga

Fig.2(xv)

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G K L G E A C V G
GAAAGTTGGGGGAGGCTTGCGTGGGG

E R D P G E Q P P
AGAGAGACCCGGGTGAGCAGCCTCCA

S K H R T R G S C
 D E G I L
CCAAGCACAGGACGAGGGGATCCTGC

R R E V R G S G *
 A R
GGCGAGAGGTAAGGGGGTCTGGGTGA
 AGATGAGGCCCTTTCCCCTCCTTCGG
 TTAGTGCTCATTTCACCCACTGCAAA
 ATCATCAAGTTGCTGAAGGGTCCAGG

 V L P A K L
 G P A G *
TGCCCTCAGGTCCTGCCGGCTAAACT

CTGCTGGGTCAGACCTGGAGGCTCAC
 TACCATCTGGGCAACAAAGAAACCTA
 AGCTCCCACAACCACAGCTTTGGTCC
 ATATACCCCAGTGTGGGTAGGGTTGG
 AGAGTCTCTTTAAATAAATAAAGGAG
 cagtgtgtttgggggcctatgtgctgg

Fig.2(xvi)

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Fig.3

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GCGGCCGCTG	CAGTGATTAC	TCACCGCGTG
TTTTTCCGTG	GGGGGATGTG	AAGAAGTTTA
GGAATGCAGG	GTTCCGGTCCC	GTTCCCCAAA
AAGGGCTCCC	TGCACGCGCT	CCGGGACATC
TGAGAAGGGA	CCAGAGGCCG	GAGACTCCCT
ACGAAACGAG	ACTACAGCGA	TGGGAGAGGT
GACCCATGCA	CCCAGAGAAA	GGGACTGGTG
AGGGCTGAAA	GAGGATGAAC	GGGCTCAGGT
TGGGTATGGG	GGCCCCGTAA	GAGGGGCGGG
GGAGGGGATC	CTGGAAAAGC	ACCAGGGCTG
ACAGGATCCC	AGATGAGGGG	GTGGGAAGCC
CACGGGCTGG	TGGGGAAAGA	GTGGGGGGCT
GTAAC TGGGC	GGAGGCCGGC	CGGGCGGGGC
GTGCGGGGCC	CACGATCAAC	CCCCCCCCAG
CGGGGCGAGC	GGCGCATTAG	CGCCTTGTCA
CGCTGTCCGC	GCCCAGTGAC	GCGCGTGAGG
CGCCCCCGCC	CCATACCGGC	GTTGCAGTCA
GGGTCGCCCCG	GGCCCCGTCTG	CCCAATCCGC

Fig.3(i)

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GCGCACCCCA	CCCGCGGGCC	GCTGAGTGGA	60
GGGAGAACTC	TTCTGCACCG	ATGGGAACTA	120
GGACACACCT	CTCCCCATAA	GCCCACTCAT	180
CCCATATCCA	ATACCCGCAG	ATATGATAGT	240
CCCTGCCTTC	TGGCTTTCCC	CCCCCCTGC	300
GGCATGAAGG	CTTAGGGTGG	GGATCGGTAG	360
GCAACTTTCA	AACTCTCTGG	GGAAGGAAGA	420
ACTGCTCAAT	GTGTGTGTGG	CGGACCAAAG	480
GAAGGTGGAT	AGGAAGGATC	CCGGTAGACT	540
CGAGCTAGGA	ACCCATTCGG	AGTTAAGGGT	600
TGGGACGGGC	GGGACCAGAG	AGGGAGGTCC	660
TCGCGCAGGA	GGATGGGACG	TTCAGGAGTG	720
GCGCGGTGCC	CGCGGGCGGT	GGGAAGGCCG	780
GGGCCGGGCC	GGGCCGGGGG	CGGGGCCGGG	840
ATTTCGGCTG	CTCAGACTTG	CTCCGGCCTT	900
ACCCGAGCCC	CAATCTGCAC	CCCGCAGACT	960
CCGCCCCGTTG	CGCGCCACCC	CCATGCCCGC	1020
GCGGCGGCCG	CCGCGGCCGC	TGTCCTCGCT	1080

Fig.3(ii)

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GTGGTCGCCT	CTGTTGCTCT	GTGTCCTCGG
GTACCGTGCG	CCCTGCTCCC	CACCTCCCCA
AGTCGCGGGG	GATGGAAGAA	GGGGCGCGAG
GGCGGCCCTC	GGGGCGCCCT	CACCTGTGGG
AGTACCCCGT	TATACATCAG	AGGCCTCTTA
AGGCTCAGTT	TGAAGGACAT	CGCAGTGTCC
GCTTCGGGGC	GCACGCCTGT	GTCTTGGATA
GGGCGCACGC	TTGGGTGCGT	TGGGTTGGGT
GAAGTGATGA	TCCCCGGGGG	GAGGGTGGGG
ATGCGGCCCC	GCGTCCCTCG	GGACTTGCCT
CTATAGCAGA	CTCCATGCTT	TGGTATCCTC
CGGTCTCATT	CAGGCTGCGC	TGGGTTGAGA
CGAGAGCAAG	CGTGTCCGGG	CACCGCGAGC
GGGGGTCAGC	TGCCGAGAGA	ATCCCACTGT
ATCACCCAAC	GCACACATCC	CCGCCAGGAT
CACACCCAAA	GACACACAAA	AGAGCCCCAC
CGCGCGCTGC	AGCCCAGATG	CGTATTCGCA
ACACACACAC	ACACACACAC	ACACACACAC

Fig.3(iii)

SUBSTITUTE SHEET (RULE 26)

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GGTGCCTCGG	GGCGGATCGG	GAGCCCGTGA	1140
GGGAAGCCGG	GATCCGGCGC	CCCGGGGGGT	1200
CGCCACCTGG	ACGTCCCGGG	AACAAAGGAA	1260
GCTCATGGCA	CCACCACCCA	GCCTCCCAAG	1320
TCTGTATCCC	CTTTGCGAGG	CTGTCTGGCC	1380
TGGGACCCCC	CTCCTTCAGG	GTGCTGGGAC	1440
TCAGAGCGGA	AGGGAAGCCT	CCCTGGCCGG	1500
GCTGGCGCAA	AGTGGGGTCC	CCTCCCCCAT	1560
CGTTATCGTG	AGCCCTCCTG	TCCGCCTGGC	1620
CTCCGTGGGG	TCGGCGCCGC	CCCCTCCCCC	1680
GAAGTCCTCT	CCACTGGTGG	GGCTCACAAC	1740
GCCTCTAGCG	ACTGAAATTT	CGGTGAGGAG	1800
CCAGACTTCA	TTGTCTAAGG	GGCACCCAGT	1860
CCCAGGAGGA	ACTCCTGGCC	TTGAGCCCCC	1920
GCGGTCTCCA	CATCCAGACC	CTCTCTGGGA	1980
TGGCTTATGT	CCCGTCACCC	TGCCCTCCGA	2040
CACCATCGCG	GCGCTCGCAT	TCCATCCTCT	2100
ACACACACAC	ACACACAGAC	ACGCACACAC	2160

Fig.3(iv)

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ACACGCACGC	ACACACACGC	ACGCCCCGCAC
GCAACACCGG	GGTACGCATA	TGGTTGAGTG
ACCCCATCCG	GAGACACAGG	CCACACCGCA
TAGTAGTCTT	GTGCAGTTTG	TCCGCGGTGT
ACAGGAACCT	ACACTCCTGC	TTGCCCAAGG
GACCTTTCCG	GGGAGTTGGT	GTTGCTGCCA
GCGCTAAGCT	TTGTTTCCGG	GCGGGCTGCA
TGGCGCGTGT	GTTTTTTTCTT	TTAAGGGGGA
TGCAATCTGT	TTGTACTTAC	CGTGTGTCTT
AAAGTGTATG	CAGGTACCAG	CGGGACAGGA
GAGGCCACCT	TCCCGTTGGC	CTTTCAGGGA
GTGTTCTTTT	TAATAACGGC	AGCAACTCCG
GGCCCCGGCT	TTGTGGAAAG	GAGGGGAAGA
GGCTTAGGGG	GCTGTCAGCT	GCTGCTCTGT
AGTGGCTTTG	GCCCATTTGT	TGTGGAAGCC
TACTCCAGAG	TCAGGCTTCT	CAGTCCGAGC
GAATCAGGGA	AGGGGGTGCC	AGGTGGACTA
AAGGAGAAAG	CTTGGGCTTG	CCCCCTCCC

Fig.3(v)

SUBSTITUTE SHEET (RULE 26)

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TCGTGGTCCC	ACATTTATTT	CACAGGGGAG	2220
CACTGGAGAT	CTTTCCCCAC	CACTCTCAGG	2280
GGGGCACCAC	GCTGCGCTGC	TGCTCTGGGC	2340
CTGTGGACGC	CCTCCCGCTC	TTGTCAGGGG	2400
CGGCTGGGCA	GGTGATGTGG	TGACACCCGG	2460
AGCCTGGGTA	GTTTTTGAAT	GCCACCAATA	2520
GAGCAACAGG	CGAAGGTGGC	GGAGTGGGGG	2580
GAGAAATTAA	ATAAGAGGTT	CTCACACCTC	2640
AACACCTGAC	CAGCCAGCCG	GTGGGTCGTA	2700
GATGGGGGCC	CCTGGGGTAT	GGCTGGGATG	2760
ATCTCACACT	TTTCCCTTTT	AAAACACATG	2820
CATTGGGAAA	GGGGGAAATA	AGCTTGTATA	2880
GGGAAGAAAA	AAGGAGGGGT	GTCTCCTCCA	2940
CTAGCTTGGC	ATGTGTGTGC	CCCAGTCCCC	3000
AAGAGGGAGA	CTGGAGTCCT	CTATCTCTGG	3060
CCAGAGAACG	TCTTCCCTGT	TTTATGGAGG	3120
CGTTCTGCTG	AGGACTGTAC	CAGTCGCTCG	3180
CCCTCAAGCC	ACGAAGGGCA	GCTGCTAGGC	3240

Fig.3(vi)

SUBSTITUTE SHEET (RULE 26)

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TAGTGTGGTA	AAAGGGCATT	ACTCCCCAGC
CAGACAAATG	CTGGGGAGGG	ACAGAGGGGT
GGTCCCCGGT	CGGGCAGTGC	CTCCCACCCT
GGGTGGGCCG	GGGTAGAGAC	GCTGGCACGT
GCGGGCGGCT	GGCTGCCTGG	GACCTCCGGG
GCCTGCTCCT	CCTGCTCCTT	CGCACGGACG
CCCAAATGCA	ACTGCGATTG	CAGGCTTCGC
CCTGGGAGAA	GTCATTCAGG	GCCCAGACTA
GGGCATGAAG	GACCGTCCAG	GGCTGCAGTT
GCAGCCTCTG	TTCTCCGAGC	CTCTTTGGAA
AATACTCTTT	TCCTCTCATC	CCATCCCGGG
TGCAGTCTTC	CCTAACCTTT	TCTTTGCTTC
CCTCTCCCCT	TGCCCAACTG	GGGCTCCAGC
CAGGGCCTCT	CTGACACACA	GGGTTGTAGC
CTCTTTTGCT	TCTGAGACTT	AATTTTTTTC
TCTCTGTACA	GCCCTGGCTG	CCCTGGCACT
ACAAACCTAC	CTGCCTCTGC	CTTTCCAGTG
AGTAGTTAAG	TGTTTTGCTG	TGTCTTTATT

Fig.3(vii)

SUBSTITUTE SHEET (RULE 26)

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CAGGACCCCC	CAGAGAGTCC	CCTTCCTGGC	3300
GTGATCATTG	CCCAGGAGTG	CAGACAGTGG	3360
GCTGAGGGGG	GCGCCCAGGC	AGGAAGCGGT	3420
CCCAGTTCAT	GCCGAAGGAA	TTCTGAATTA	3480
GCGGCCCCCT	GGCCCCCGCC	GCTCCGTCTG	3540
CTGAGACCTC	CGCTGAGCCC	TGGGACAAGC	3600
AAGACCCGCC	TCCTCCCAAG	GCCAAATTTG	3660
GAACCATGTT	GGTGCCACCT	CATCCATCTG	3720
TAGCTTCTTA	ATAGGAACCT	GGGGGTGGGT	3780
ATCGGTTTTG	TTTTTGTTTT	TGTTTTTTCC	3840
ACTGTTTTCC	TCCCTAAGGG	TTGAGAGCCC	3900
TACCCCAGGG	CCTTTGCACA	TGGAGTCCCA	3960
CTTACTGCAT	TTGGCTCTTG	GTAAGTGTCC	4020
CCCAGCTCCC	TCTCTTCTCC	TCCCCCCTTT	4080
TTTTTCTTTT	TGGCTTTTTG	AGACAGGGTT	4140
CATTCTGTAG	ACCAGGCTAG	CCTCAAATCTC	4200
CTGGCACTAA	AGATGTGGGC	CACCACAACCT	4260
CCTATAGTGA	CCTCAGTTCC	TGGCATATTG	4320

Fig.3(viii)

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TAGGCGATGG	ATGGATGAAT	GGATGGATGG
CTTGAATCGT	CCTGAGTGAA	AAAAGAGACC
GGCAGCCTGG	CCTGCTGGTC	TCATGGGAGC
CACCCTGCCA	TCCTGTGTGG	CTGACAAGAA
AGGGAAGCTT	GGAATATGTT	CCCCTCCTCA
CCAGCCTATG	AGTAGGGCAG	CTGTGGGCTG
GTCCCTCAGG	GTGGGTCACA	GGATTGAGGT
AGGAAATGAT	TGTGGAGAGT	CAGAACTCCT
GCTTCTGTGG	CTGTCCCTTC	TCTTGTGGTC
TGTGAGGAGG	GCACGGGGAA	AATGAAGGCT
CCAACAGGGC	TCACCTCTCC	TCTGGACAGG
TTTGATTCCC	TTCCTTTGGT	CTCCTGGGAT
TTTTAGATAT	GTCCATTCTC	CAGAAACACA
ACCACCAGGA	CAGACAAAGA	ATTGGAGAGG
TGGCTTATGT	GTAATCCCAG	AACTCTGGAC
CAGTGTGTTC	TAGGTAATGA	GACCCTGTCA
ATGTTTATAG	GCTGTGAGAC	AGCTTGGTGG
CCTCAGCCCC	ATCCCTAGGA	ATCCATGGTA

Fig.3(ix)

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ATGGATGGAT	GGATGGTTGG	ATGGAGCAAG	4380
TCAGAGAACT	GAATGGAGTT	AGGTTCCCAG	4440
TCCCTGTGAA	ACTTCCCCCA	CACCTCCCAC	4500
AGGCCAATGG	CCAGATGGGG	ACACAGACTC	4560
TATCCTAGGC	CTTGTTGTCC	CCCTGAGGGC	4620
CCCTAAGGTT	GGGTAGGCAA	GAAGGGGGTG	4680
CATTTCCAAA	GTGGCCATCA	CAGTGGCCCT	4740
GTTGGGAGTT	GTAGAGGGCC	TTGCATGTGG	4800
CTTTGCACAG	TCCCCTCGTG	TGTGCTGGGA	4860
CAGCCCCTCA	GCTTGCCCTT	CACGGTTCAC	4920
CTCTCACTGT	ATGCACAGAT	TGGCCTCACA	4980
GACAAACATT	TACCAGGGTA	GGATTTTACA	5040
CTTGTGAGGT	TAGGGTATCA	GTGAAAGGAC	5100
AAGGAAATTG	GTAAGCCAGG	CCATGCTTGA	5160
GCTGAGGCAG	GAGGATTCCA	AGTTTCAAGA	5220
AGAAAAGAAA	AGAAATAAAG	AGACAAGAAA	5280
GTAAGGGGCA	CTTGCCTCCA	ATCAAGATGA	5340
GAAGGAGAAA	GCAAACCTCCA	GCTGCTGACC	5400

Fig.3(x)

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TCCATACATG	TGCTCCAATG	TGCACACACA
TTTGCTTAGA	TTTGAGTAGG	CATTTATGAC
GAAAATATAC	CTGTTTGTAT	TTGGTTTGGT
GCTTCTCTGT	GTAGTCCTGG	CTGTCCTTGG
ACTCAGAAAT	CCGCCTGCTT	GTGCTTCCCA
TCAGCAAAAT	TGCATACTTT	AACCCCAGTA
ATTCCAGGCT	AGCCAAGGAT	ACAGAGTGAG
CCAAAATGTA	TTTTGTGCTT	GTGTATGTAC
ACAACCTTGTA	GAAGTTCTCT	CCGTTCCACAG
AGGCTTAGCC	ACAGTCTTCT	TTATGTACTG
GAATTAATTT	TTGAGATAAG	GTCTCTTGTA
AAGGTCATCT	TGAGCTGCTG	GTACTCTTGC
GCAGCACTTC	TCTGGGGAAG	GGGCTGGCCT
GAGTGCTTGG	GTCTCGTTGT	TTCTTTTCTT
GACTTCCTGA	CTCTTGAAAC	ATCCAGGCAG
GCCTAACAAA	GTGTCGTCTT	TGACCCCAGA
CCTTCTCATC	GGCTCCTCCC	TGCAAGCTAC
CACCGCTGAG	GGGCTCTACT	GGACCTTCAA

Fig.3(xi)

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CAGGGAGACA	TAATCAATTA	ATAGGATGTA	5460
TGATGTTTTA	AAATTTTTTAT	TTGATTTTTAT	5520
TTGGTTTGAG	TTTTGTTTAT	TTGAGACAGG	5580
AACTCACTCT	GTAGACCAGG	CTGGCCTTGA	5640
AGTGCTTAGA	TTAAAGGTGT	GCACTGCCAT	5700
TTTGGGAGGC	AGAGGCAGAC	TAATGTGTGA	5760
ACCCTATTCT	TACCCTCCCC	CCCCAAAACC	5820
ATGTGTGTTG	CAGCACGTAA	ATGTCCAAGG	5880
TCTAAGTCCT	GAATTCAAAC	TAAGGTCCTC	5940
AGCCATTTCA	CTGGCCCTGG	ATTGACTGAT	6000
GCTCTAGCTA	GGCTCAAAC	ATGAACTCCC	6060
TTCCACCCCA	AGTGGTGGAA	TGATACTCAG	6120
TGGCCTTGAT	TTTGTTGCCT	CAGCTTCAAT	6180
TATCTGTGAA	ATGGGTGAAC	ACCTGTTCAA	6240
GGTGAGGGAC	TTGAAGTGGG	CTCATCCCAT	6300
CACAGCTGTA	ATCAGCCCCC	AGGACCCAC	6360
CTGCTCTATA	CATGGAGACA	CACCTGGGGC	6420
TGGTCGCCGC	CTGCCCTCTG	AGCTGTCCCG	6480

Fig.3(xii)

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CCTCCTTAAC	ACCTCCACCC	TGGCCCTGGC
GTCAGGAGAC	AATCTGGTGT	GTCACGCCCCG
CTATGTTGGC	TGTAAGTGGG	GCCCCAGACA
GATTTAGAGC	CTGGGTCTTC	TGTCCTGGGG
CATGGTCATA	CCCAGCACAG	GCATTGCAAC
TGTGTACCCC	ACAGCTTTAG	AAAAGCTGTC
CCTTTAACAT	CAGCTGCTGG	TCCCGGAACA
GTGCACACGG	GGAGACATTC	TTACATACCA
TACCCAGCCA	AGCCTTGCTG	TGTGACTTCT
TTCCTGTTTA	TGAACTCAAA	AGGGACTCTC
CACATGTGAG	GAGTACCACA	CTGTGGGCCC
CCTCTTCACT	CCCTATGAGA	TCTGGGTGGA
TGATGTCCTC	ACACTGGATG	TCCTGGACGT
GCCCTAGACC	TTATAGGGCG	CCTCCCCCCC
GTCTTAGCCA	CAGCCACGGT	GGTTGCAGGA
TTTCCCCCAA	GACAGTCAAG	ATTTTCCCCT
CTCTGCAGAG	AACACCTGGC	CTGACCACCC
GAGTCCTAGG	GGACTGAGAG	GAGGCGCCCA

Fig.3(xiii)

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CCTGGCTAAC	CTTAATGGGT	CCAGGCAGCA	6540
AGACGGCAGC	ATTCTGGCTG	GCTCCTGCCT	6600
CTCAGAGATA	GATGGGGGTT	GGCAATGACA	6660
CAGAGCCATG	GGCTCTCACT	TGCATGCAGG	6720
TCTAGGGACA	GCTGTGGCTG	CACTGTCCCC	6780
ATGTTTTTCCT	TGTAGTGCCC	CCTGAGAAGC	6840
TGAAGGATCT	CACGTGCCGC	TGGACACCGG	6900
ACTACTCCCT	CAAGTACAAG	CTGAGGTTGG	6960
GGCAATACTT	ACCTTCTCTG	ATCAAATATG	7020
GCACCTCCAC	AGGTGGTACG	GTCAGGATAA	7080
TCACTCATGC	CATATCCCCA	AGGACCTGGC	7140
AGCCACCAAT	CGCCTAGGCT	CAGCAAGATC	7200
GGGTGAGCCC	CCAGTGTCCA	CCTGTGTTCT	7260
ATCCCCCAG	ACTTTTTTGGT	TCTTCTAGAG	7320
CAGTGGTTGT	TCATAACTTA	ATGCAAAGAC	7380
CCCCACCCCC	AACACACACA	TACACACACA	7440
TCCCTCTCTA	CAGCCCAGGT	G TTCAGAAGG	7500
GGTCTGAAGG	CGCCCCAGGA	AGCCGAGGCC	7560

Fig.3(xiv)

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TTGAGCTGGG	GGGGGGGGCG	AGGGTTGGAG
GGGCCTAATC	TAATTAGGGT	GTTCCCAGCC
GTGCCTCACT	GAAGACTCAG	GGGAGAGATC
GGGTTCCTGG	GTGCCCCTGG	CTCATTCCCA
TAACCCTCAG	TTGTGCTCTG	TGGCTGGCAC
CAAGGCATCA	GAGGTGGACA	TGGGATGGGG
AAGGTGGGGT	GATATACAAT	AAAGCTTGTC
GATCACAATT	GTTGACATCA	CTCTGGGACA
AGTAGCTTTA	AGAGTCAGCT	TGTGACTTAA
GTGATGCTCG	CCTCACTCCC	TGTTTAGTGA
GTGGGCTGCT	CTGTCCCCTT	GAGGGCAGGA
TGGTAGCAGC	AACTGCTGCT	GGCTGTTTCT
CTGGGTGAGT	AGCTAACAGG	GGTGGGGGCG
AGCCACTGCA	GCCTAGATTA	CACCACTGGG
AGTCCTCAGA	ACTGGGAGCA	CTGTTGCCAG
AGGGGAGGCA	GAGGCAGAAG	GATCTCTCTG
AGCTCCAGGC	CAGCCAGGGT	GCGCAGTAAA
TGACCAGGCT	TGCTCCACCC	CCAGTGACCA

Fig.3(xv)

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GCACGAACTG	GATGATCCCT	GAGCACAAC	7620
CAAAGCAGCC	TGGGCCATTT	AACCCTTCAA	7680
AGCTTGTACT	CTCTCCATGG	TCCCCCAGGA	7740
CATCCAGAGG	TTTTGTGTCT	TCCTGGCATC	7800
AGCTGCCCCG	TGGAGGCTCT	TGGTAATGTA	7860
ATACATAGGG	ATGGAGCCAA	ATAGCACCTC	7920
ACCCTGACGC	TCAGAAAGCC	TACTCATGAT	7980
TGTAGTGAGA	CCCTAGCTCA	AAACACAGAC	8040
TACTGGAACT	CAGGGCCTAA	TAGGTGCTGG	8100
GATCTCTGCG	CTAATCTCCA	CCCCAGCTGG	8160
ATGTGTGTCT	TCCATCAGAG	ATAGGACCCG	8220
GGAATATTAA	ATGACAGTAA	TCTATCAGGC	8280
TGGTCTGGAA	AACGCAGATA	GGGTCATAGG	8340
TGTTCTGTCA	CTAGGCCATT	CTCACCAAGC	8400
CATTTAATGC	CAGCATTTAA	TGCCAGCATT	8460
AGTTCAAGGC	CATCCTGAAT	TTACATAAAG	8520
ACCTTGTCTC	AAAAAACAAA	GCATCTTTAG	8580
CGGACCCCCC	ACCCGACGTG	CACGTGAGCC	8640

Fig.3(xvi)

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GCGTTGGGGG	CCTGGAGGAC	CAGCTGAGTG
ATTCCTCTT	CCAAGCCAAG	TACCAGATCC
AGGTGCCCCGT	CCCGCCCCCG	ACCCGCCCCT
CACCGTGCAG	GTGGTGGATG	ACGTCAGCAA
GCCCGGCACC	GTTTACTTCG	TCCAAGTGCG
AAAGGCGGGA	ATCTGGAGCG	AGTGGAGCCA
TGAGCACCTC	TCCAGGGCTG	GCTGGCCCAT
CCCACCCTTT	TTTTGAGACA	GCGTCTTCAG
TAGTCAAGGA	TGACCTCGAG	CTCCTGGTCT
GGCCATCACC	ACCTTTGGGA	GACTAGCCAT
GATGGAGTAC	AACAGTGTGA	CCTCTTGTA
AATATCCTAG	GCTCTCTAGA	GGTTAACTTT
TCACATGGTC	CCACAGAACC	TTTTGTCACA
CACATAAGGG	TCTCTACTGC	TGGCCCACCC
CTTAATATTT	GCAATCCTCC	TACCTCAGCC
CAAGTTTCTC	TTCTCTGGGT	CCCTTTCTTA
GTCCTGAAGA	CTCTCCGAGC	CCATGGATCT
AATGTCTGGC	CTCAGTTTCC	CCACCTGTCA

Fig.3(xvii)

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TGCGCTGGGT	CTCACCACCA	GCTCTCAAGG	8700
GCTACCGCGT	GGAGGACAGC	GTGGACTGGA	8760
GACCCCGCCC	CCCGCATCTG	ACTCCTCCCT	8820
CCAGACCTCC	TGCCGTCTCG	CGGGCCTGAA	8880
TTGTAACCCA	TTCGGGATCT	ATGGGTCGAA	8940
CCCCACCGCT	GCCTCCACCC	CTCGAAGTGG	9000
GGAATCCCCA	ATCCATCCTG	TTCCTTCCCC	9060
GTAGCGCATG	CTGGCCTTAA	ATTCAGTATG	9120
TTTTGTCTCC	ACTTAGAGAC	AATGGCCAGT	9180
GGAGTCTATT	TAGCCTGTCA	TTTGGTGACA	9240
GAGAACTGAA	GACAGGCTGT	TTTTAACCCC	9300
ATATAAAATA	GAGACTATTA	CAGCCAGTTA	9360
CAACCTATAG	ACCACAGTGC	CTGTGCCTAC	9420
CTCCAACCCT	TAAAAGGTAA	CCTAGGCAGC	9480
TCTTGAATGC	TCAGAAACCA	GGCATTAAAC	9540
AGGTGGGAGG	GCCTAAAGAT	GACTTCCTTT	9600
GCACTCTCTA	ATATGAAATA	TATTGCATAA	9660
GGTTTAGGCA	GCACAGTCGG	TCCAAGACAC	9720

Fig.3(xviii)

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TTCATTATTT	GCAGGCAGTA	TAAGAAGAAG
CTAAGACAGA	ATACTTCTAC	ACTGAAACTG
TGATGATGAA	ATAATGGGGA	AACTGAGGCT
ACCAGCTCCA	GGAAGCTCTC	CAGCCCCCAT
GAGTGAACAC	AGCTGGGAGG	GGCTGGAGCC
ACCTGCGATT	CTTGCACGGG	AGCCAGCAGG
CCGGGGGGTAG	GGTTGGAGGG	AGGTAAGCAG
CCTGTCAGCG	AGTCCCCAGT	TTTATTTATG
TGCTGGGGGA	TGGCTGCGGC	TGGGGATTGG
CAGCCCCTC	CATGTCACAC	CCGTGCATTC
TTCTGTGCTG	TCTGTCTCTA	TTTCTGTCAT
TTAATATAAC	TACGTTTTAA	AAATTGCTTT
GTGCCACAAC	ACACACGTGA	AGGTTAGAGA
GGGACTAGGG	CTGGCGACAA	GAGCAATTAC
CTTCCCATCC	TGTTTGGATA	GTCATAGGTA
TAGCTATCCT	GCCTCAGCCT	ACCAAGTGCT
TCCCAGTGTC	TGGGGGTACA	CAGTCCCAAG
TGCCCCTTGC	TTTGTCCGTG	TCCCTAGAGT

Fig.3(xix)

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CTCCCATCCC	CCACCCGCTT	CCTCCGGTCC	9780
AACTCTCGCA	GACGCATATG	CTCACTTTAA	9840
CCGAGAGATT	CCTGGAGGAA	GAGGGTCAAA	9900
CCGGGCCTCT	CCAGGTTCTG	GGCTTGGCGG	9960
TGGGAGCTTT	GGCCCTTGCT	CGTGCCCAGC	10020
CGGCTGCGTC	CGCCCGAGAG	ACTGAAGAAG	10080
GGGCTGTGGG	GGCCGAAGCT	TGTGCCAGGG	10140
GCGTGAGGCC	GATGTCCTTA	TCCGCTGGCC	10200
ACCCAAGGGC	TGGCTTCCCA	CTCAGTCCTC	10260
TCTGAGGCTT	ATCTTGGGAA	CCCGCCCTTG	10320
TCACTTTCCC	AGAGCCTTTT	TTTTATGCTT	10380
TGTATAATGT	GTGTGCCTTC	GTGAGCGTGC	10440
ACTTTGTTGA	GTAGGCTCCT	TCCACCATGT	10500
TGAGTCATCT	CGCCAGCCCC	TCACCCCTCA	10560
ATCGAAGGTA	AATCGCTGGC	TTTAATTTTCG	10620
GTGCTACCAC	GTTTGTGGGA	GGGGCTCTCC	10680
ATCTCTGCTT	TCTAGGTCTT	TGTCTTAGTT	10740
CTCCGGCCCC	ACTTAGTCTC	CATTGATTTC	10800

Fig.3(xx)

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CTTTCTGACC	GAATACTCGG	TTTTACCTCC
CCATCGCCGT	GGCATTGCCA	TTCCTCTGGG
CAACTTTCCC	CAGCCGAAGC	TGGTCTGGTA
GCTGGCCGCG	CCCCAACACT	GCCGCTCCAT
GGGTGTGCGA	GCCGCGGGGC	GGCGAGCCCA
AGTTCCTCGG	CTGGCTCAAG	AAGCACGCAT
ACCAGTGGCG	TGCTTGGATG	CAGAAGTCAC
GGGAGGCTTG	CGTGGGGGGT	AAAGGAGCAG
CACAACACCG	CACTCTTCTT	TCCAAGCACA
GGGTGCGGCG	AGAGGTAAGG	GGGTCTGGGT
CCTTTCCCCT	CCTTCGGTGT	TGCTCAAAGG
AAGAGCCCCA	GGTTTTACTG	CATCATCAAG
CTTTTCTGCC	CTCAGGTCCT	GCCGGCTAAA
CAGACCTGGA	GGCTCACCTG	AATTGGAGCC
TACCAGAGGC	TGGGCACAAT	GAGCTCCCAC
ACTTGGATAT	ACCCAGTGT	GGGTAGGGTT
TTAAATAAAT	AAAGGAGTTG	TTCAGGTCCC
GGGGTGGGGG	GA	

Fig.3(xxi)

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CACTGATTTG	ACTCCCTCCT	TTGCTTGTCT	10860
TGACTCTGGG	TCCACACCTG	ACACCTTTCC	10920
TGGGAGGCCG	CCGTCCCGCG	CGCGCCTCCT	10980
TCTCTTTAGA	GCGCCCGGGC	CCGGGCGGCG	11040
GCTCGGGCCC	GGTGCGGCGC	GAGCTCAAGC	11100
ACTGCTCGAA	CCTTAGTTTC	CGCCTGTACG	11160
ACAAGACCCG	AAACCAGGTA	GGAAAGTTGG	11220
AGGAAGAGAG	AGACCCGGGT	GAGCAGCCTC	11280
GGACGAGGGG	ATCCTGCCCT	CGGGCAGACG	11340
GAGTGGGGCC	TACAGCAGTC	TAGATGAGGC	11400
GATCTCTTAG	TGCTCATTTT	ACCCACTGCA	11460
TTGCTGAAGG	GTCCAGGCTT	AATGTGGCCT	11520
CTCTAAGGAT	AGGCCATCCT	CCTGCTGGGT	11580
CCTCTGTACC	ATCTGGGCAA	CAAAGAAACC	11640
AACCACAGCT	TTGGTCCACA	TGATGGTCAC	11700
GGGGTATTGC	AGGGCCTCCC	AAGAGTCTCT	11760
GATGGCCAGT	GTGTTTGGGG	CCTATGTGCT	11820
			11832

Fig.3(xxii)

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MURINE NR-6 GENOMIC STRUCTURE

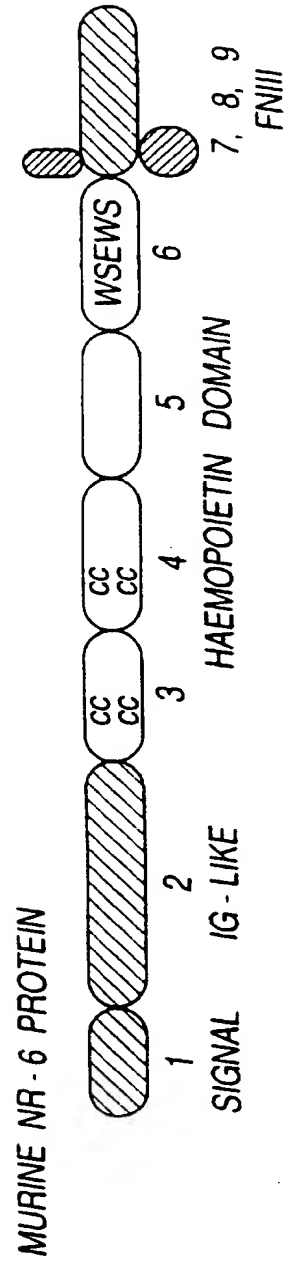
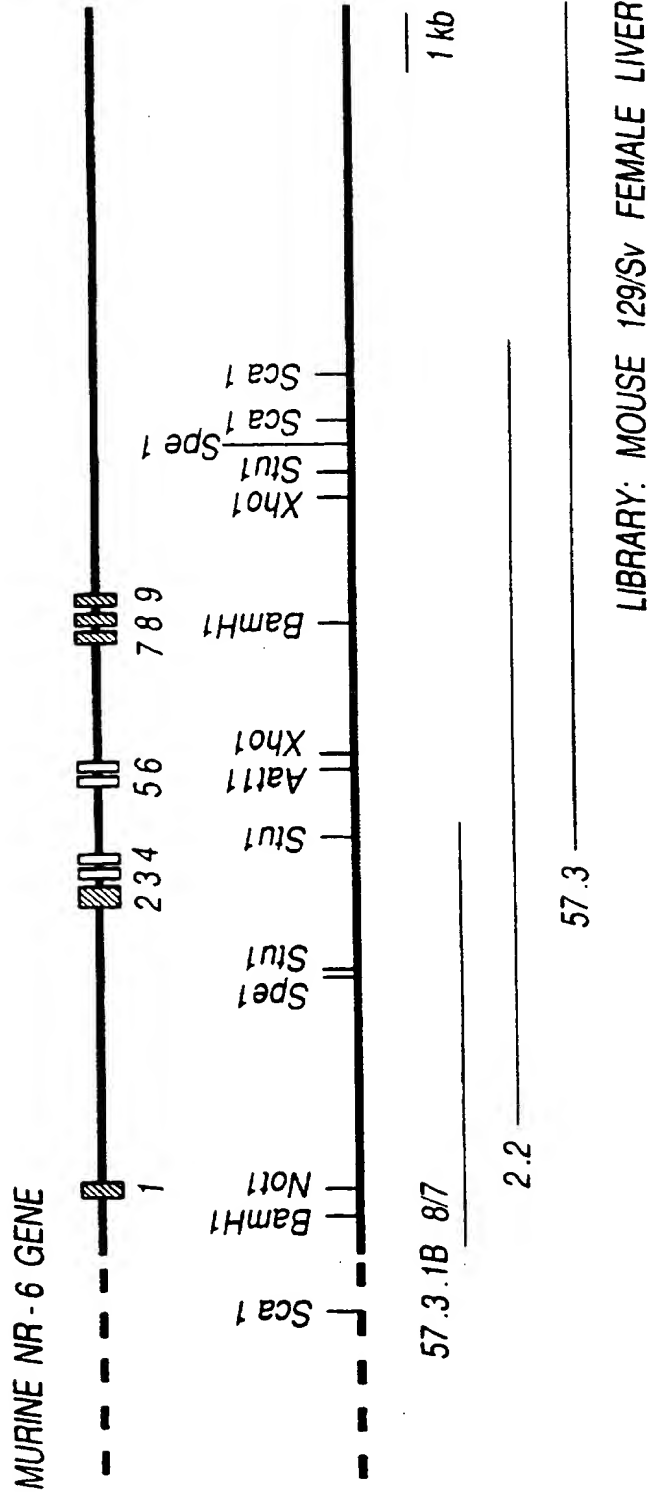


Fig.4

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TARGETING THE NR6 LOCUS BY HOMOLOGOUS RECOMBINATION

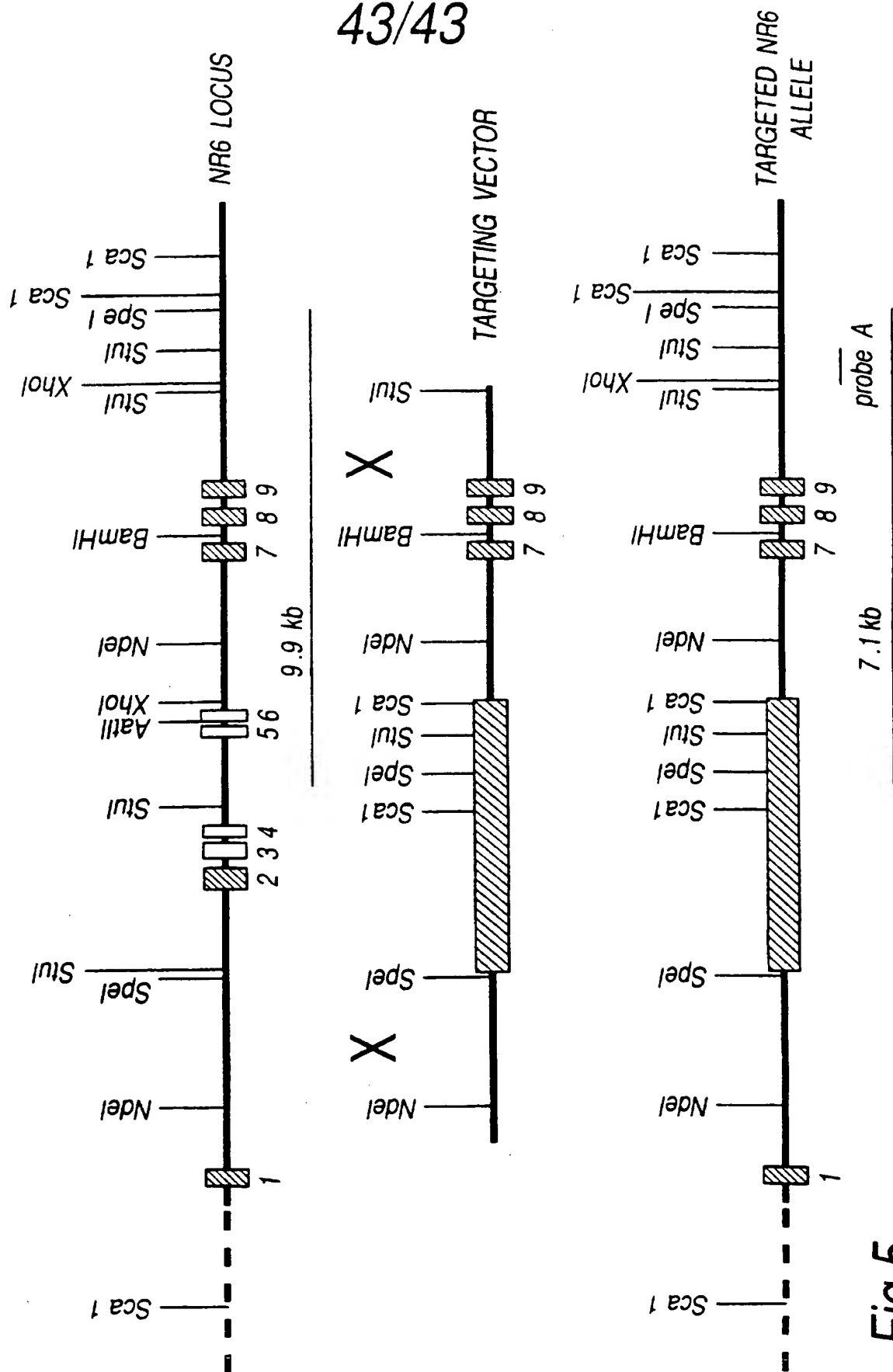


Fig.5

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C12N 15/19, C07K 14/715, A61K 38/17, C07K 16/18, A01K 67/027	A3	(11) International Publication Number: WO 98/11225 (43) International Publication Date: 19 March 1998 (19.03.98)
(21) International Application Number: PCT/GB97/02479 (22) International Filing Date: 11 September 1997 (11.09.97) (30) Priority Data: PO 2246 11 September 1996 (11.09.96) AU (71) Applicant (for all designated States except US): AMRAD OPERATIONS PTY. LTD. [AU/AU]; 576 Swan Street, Richmond, VIC 3121 (AU). (71) Applicant (for GB only): DZIEGLEWSKA, Hanna, Eva [GB/GB]; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): HILTON, Douglas, James [AU/AU]; 244 Research Road, Warrandyte, VIC 3113 (AU). NICOLA, Nicos, Antony [AU/AU]; 56 Churchill Avenue, Mont Albert, VIC 3127 (AU). FARLEY, Alison [AU/AU]; 27/9-19 Miller Street, North Fitzroy, VIC 3068 (AU). WILLSON, Tracy [AU/AU]; 26 Fortuna Avenue, North Balwyn, VIC 3104 (AU). ZHANG, Jian-Guo [CN/AU]; 3 Karri Crescent, Hoppers Crossing, VIC 3029 (AU). ALEXANDER, Warren [AU/AU]; 13 Park Street, Moonee Ponds, VIC 3039 (AU). RAKAR, Steven [AU/AU]; 26 Riverside Avenue, Avondale Heights, VIC 3034 (AU). FABRI, Louis [AU/AU]; 8 Laver Court, Mill Park, VIC 3082 (AU). KOJIMA, Tetsuo [JP/JP]; 1-8-1-302 Minami-Rokugou, Ota-ku, Tokyo 144 (JP). MAEDA, Masatsugu [JP/JP]; 1-6-2-606		Kasuga, Tsukuba, Ibaraki 305 (JP). KIKUCHI, Yasufumi [JP/JP]; 1-29-5-110 Komatsu, Tsuchiura, Ibaraki 300 (JP). NASH, Andrew [AU/AU]; 24 Green Street, Northcote, VIC 3070 (AU). (74) Agents: DZIEGLEWSKA, Hanna, Eva et al.; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 30 April 1998 (30.04.98)
(54) Title: A NOVEL HAEMOPOIETIN RECEPTOR AND GENETIC SEQUENCES ENCODING SAME		
(57) Abstract <p>The present invention relates generally to a novel haemopoietin receptor or derivatives thereof and to genetic sequences encoding same. Interaction between the novel receptor of the present invention and a cytokine ligand facilitates proliferation, differentiation and survival of a wide variety of cells. The novel receptor and its derivatives and the genetic sequences encoding same of the present invention are useful in the development of a wide range of agonists, antagonists, therapeutics and diagnostic reagents based on ligand interaction with its receptor.</p>		

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INTERNATIONAL SEARCH REPORT

Internatic Application No
PCT/GB 97/02479

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/19 C07K14/715 A61K38/17 C07K16/18 A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE EMBL12 emb1 SEQ ID MM77631 Acc.No:W66776, 15 June 1996 "Mus musculus cDNA me17b11.r1 similar to PIR:B38252 granulocyte colony-stimulating factor receptor precursor" XP002055540 cited in the application & MARRA ET AL.: "The WahU-HHMI mouse EST project" ..</p> <p style="text-align: center;">--- -/--</p>	<p>1-10, 14-19</p>

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Z document member of the same patent family

Date of the actual completion of the international search

12 February 1998

Date of mailing of the international search report

06.03.98

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

Authorized officer

Cupido, M

INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/GB 97/02479

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ROBB ET AL.: "Structural analysis of the gene encoding the murine Interleukin-11 receptor alpha-chain and a related locus" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 271, no. 23, 7 June 1996, MD US, pages 13754-13761, XP002055539 see figure 3 ---	1-3,20, 21
X	WO 96 08510 A (PROGENITOR, INC.) 21 March 1996 see figure 2c nucleotides 1053-1068 on sheet 4/11 ---	1-3,20, 21
X	WO 96 07737 A (AMRAD OPERATIONS PTY. LTD.) 14 March 1996 see figure 8 nucleotides 1040-1055 on sheet 14/21 see claims 1,13 ---	1,3,13, 20
P,X	WO 97 15663 A (AMRAD OPERATIONS PTY. LTD.) 1 May 1997 see figure 7 (vii) on sheet 20/24 ---	1-3,20, 21
P,X	WO 97 12037 A (AMRAD OPERATIONS PTY. LTD.) 3 April 1997 see claims 1-3 ---	1-3,20, 21
P,X	WO 97 25425 A (GENENTECH, INC.) 17 July 1997 see figure 2b on sheet 12/85 -----	1-3,20, 21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 97/02479

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
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Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 97/02479

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Remark : Although claims 28 and 29 are directed to a method of treatment of the human/animal body , the search has been carried out and based on the alleged effects of the composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat' Application No

PCT/GB 97/02479

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9608510 A	21-03-96	US 5643748 A AU 3419495 A CA 2176463 A EP 0730606 A	01-07-97 29-03-96 21-03-96 11-09-96
WO 9607737 A	14-03-96	AU 3465295 A CA 2197873 A EP 0804576 A	27-03-96 14-03-96 05-11-97
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WO 9725425 A	17-07-97	AU 1574797 A	01-08-97

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(51) International Patent Classification ⁶ : C12N 15/19, C07K 14/715, A61K 38/17, C07K 16/18, A01K 67/027	A3	(11) International Publication Number: WO 98/11225 (43) International Publication Date: 19 March 1998 (19.03.98)
(21) International Application Number: PCT/GB97/02479 (22) International Filing Date: 11 September 1997 (11.09.97) (30) Priority Data: PO 2246 11 September 1996 (11.09.96) AU (71) Applicant (for all designated States except US): AMRAD OPERATIONS PTY. LTD. [AU/AU]; 576 Swan Street, Richmond, VIC 3121 (AU). (71) Applicant (for GB only): DZIEGLEWSKA, Hanna, Eva [GB/GB]; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): HILTON, Douglas, James [AU/AU]; 244 Research Road, Warrandyte, VIC 3113 (AU). NICOLA, Nicos, Antony [AU/AU]; 56 Churchill Avenue, Mont Albert, VIC 3127 (AU). FARLEY, Alison [AU/AU]; 27/9-19 Miller Street, North Fitzroy, VIC 3068 (AU). WILLSON, Tracy [AU/AU]; 26 Fortuna Avenue, North Bal- wyn, VIC 3104 (AU). ZHANG, Jian-Guo [CN/AU]; 3 Karri Crescent, Hoppers Crossing, VIC 3029 (AU). ALEXAN- DER, Warren [AU/AU]; 13 Park Street, Moonee Ponds, VIC 3039 (AU). RAKAR, Steven [AU/AU]; 26 Riverside Avenue, Avondale Heights, VIC 3034 (AU). FABRI, Louis [AU/AU]; 8 Laver Court, Mill Park, VIC 3082 (AU). KO- JIMA, Tetsuo [JP/JP]; 1-8-1-302 Minami-Rokugou, Ota-ku, Tokyo 144 (JP). MAEDA, Masatsugu [JP/JP]; 1-6-2-606		Kasuga, Tsukuba, Ibaraki 305 (JP). KIKUCHI, Yasufumi [JP/JP]; 1-29-5-110 Komatsu, Tsuchiura, Ibaraki 300 (JP). NASH, Andrew [AU/AU]; 24 Green Street, Northcote, VIC 3070 (AU). (74) Agents: DZIEGLEWSKA, Hanna, Eva et al.; Frank B. Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL (GB). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims</i> <i>and to be republished in the event of the receipt of amendments.</i> (88) Date of publication of the international search report: 30 April 1998 (30.04.98)
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CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

A NOVEL HAEMOPOIETIN RECEPTOR AND GENETIC
SEQUENCES ENCODING SAME

5 The present invention relates generally to a novel
haemopoietin receptor or derivatives thereof and to
genetic sequences encoding same. Interaction between
the novel receptor of the present invention and a ligand
facilitates proliferation, differentiation and survival
of a wide variety of cells. The novel receptor and its
10 derivatives and the genetic sequences encoding same of
the present invention are useful in the development of a
wide range of agonists, antagonists, therapeutics and
diagnostic reagents based on ligand interaction with its
receptor.

15 Bibliographic details of the publications numerically
referred to in this specification are collected at the
end of the description. Sequence Identity Numbers (SEQ
ID NOs.) for the nucleotide and amino acid sequences
20 referred to in the specification are defined following
the bibliography.

Throughout this specification and the claims which
follow, unless the context requires otherwise, the word
25 "comprise", or variations such as "comprises" or
"comprising", will be understood to imply the inclusion
of a stated integer or group of integers but not the
exclusion of any other integer or group of integers.

30 The rapidly increasing sophistication of recombinant DNA
techniques is greatly facilitating research into the
medical and allied health fields. Cytokine research is
of particular importance, especially as these molecules
regulate the proliferation, differentiation and function
35 of a wide variety of cells. Administration of
recombinant cytokines or regulating cytokine function
and/or synthesis is becoming increasingly the focus of

medical research into the treatment of a range of disease conditions.

5 Despite the discovery of a range of cytokines and other secreted regulators of cell function, comparatively few cytokines are directly used or targeted in therapeutic regimens. One reason for this is the pleiotropic nature of many cytokines. For example, interleukin (IL)-11 is a functionally pleiotropic molecule (1,2), initially
10 characterized by its ability to stimulate proliferation of the IL-6-dependent plasmacytoma cell line, T11 65 (3). Other biological actions of IL-11 include induction of multipotential haemopoietin progenitor cell proliferation (4,5,6), enhancement of megakaryocyte and
15 platelet formation (7,8,9,10), stimulation of acute phase protein synthesis (11) and inhibition of adipocyte lipoprotein lipase activity (12, 13).

20 Other important cytokines in the IL-11 group include IL-6, leukaemia inhibitory factor (LIF), oncostatin M (OSM) and CNTF. All these cytokines exhibit pleiotropic properties with significant activities in proliferation, differentiation and survival of cells. Members of the haemopoietin receptor family are defined by the presence
25 of a conserved amino acid domain in their extracellular region. However, despite the low level of amino acid sequence conservation between other haemopoietin receptor domains of different receptors, they are all predicted to assume a similar tertiary structure,
30 centred around two fibronectin-type III repeats (18,19).

The size of the haemopoietin receptor family has now become extensive and includes the cell surface receptors for many cytokines including interleukin-2 (IL-2), IL-3,
35 IL-4, IL-5, IL-6, IL-7, IL-9, IL-11, IL-12, IL-13, IL-15, granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage-CSF (GM-CSF), erythropoietin,

thrombopoietin, leptin, leukaemia inhibitory factor, oncostatin-M, ciliary neurotrophic factor, cardiotrophin, growth hormone and prolactin. Although most of the members of the haemopoietin receptor family act as classic cell surface receptors, binding their cognate ligand at the cell surface and initiating intracellular signal transduction, some receptors are also produced in naturally occurring soluble forms. These soluble receptors can either act as cytokine antagonists, by binding to cytokines and inhibiting productive interactions with cell surface receptors (eg LIF binding protein; (20) or as agonists, binding to cytokine and potentiating interaction with cell surface receptor components (eg soluble interleukin-6 receptor a-chain; (21)). Still other members of the family appear to be produced only as secreted proteins, with no evidence of a cell surface form. In this regard, the IL-12 p40 subunit is a useful example. The cytokine IL-12 is secreted as a heterodimer composed of a p35 subunit which shows similarity to cytokines such as IL-6 (22) and a p40 subunit which shares similarity with the IL-6 receptor a-chain (23). In this case the soluble receptor acts as part of the cytokine itself and essential to formation of an active protein. In addition to acting as cytokines (eg IL-12p40), cytokine agonists (eg IL-6 receptor a-chain) or cytokine antagonists (LIF binding protein), members of the haemopoietin receptor have been useful in the discovery of small molecule cytokine mimetics. For example, the discovery of peptide mimetics of two commercially valuable cytokines, erythropoietin and thrombopoietin, centred on the selection of peptides capable of binding to soluble versions of the erythropoietin and thrombopoietin receptors (24,25). Due to the importance and multifactorial nature of these cytokines, there is a need to identify receptors, including both cell bound and soluble, for pleiotropic cytokines. Identification

of such receptors permits the identification of pleiotropic cytokines and the development of a range of therapeutic and diagnostic agents.

5 Accordingly, one aspect of the present invention relates to a nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding a novel haemopoietin receptor or a derivative thereof.

10

More particularly, the present invention provides a nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding a novel haemopoietin receptor or a derivative thereof having the motif:

15

Trp Ser Xaa Trp Ser [SEQ ID NO:1],
wherein Xaa is any amino acid and is preferably Asp or Glu.

20 Even more particularly, the present invention is directed to a nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding a novel haemopoietin receptor or a derivative thereof, said receptor comprising the motif:

25

Trp Ser Xaa Trp Ser [SEQ ID NO:1]

wherein Xaa is any amino acid and is preferably Asp or Glu, said nucleic acid molecule is identifiable by hybridisation to said molecule under low stringency conditions at 42EC with

30

5N (A/G)CTCCA(A/G)TC(A/G)CTCCA 3N [SEQ ID NO:7]

and

5N (A/G)CTCCA(C/T)TC(A/G)CTCCA 3N [SEQ ID NO:8].

35

Still more particularly, the present invention provides an isolated nucleic acid molecule comprising a sequence

of nucleotides substantially as set forth in SEQ ID
NO:12 or a nucleotide sequence having at least 60%
similarity to the nucleotide sequence set forth in SEQ
ID NO:12 or a nucleotide sequence capable of hybridising
5 thereto under low stringency conditions at 42EC and
wherein said nucleotide sequence encodes a novel
haemopoietin receptor or a derivative thereof.

10 In a related embodiment, the present invention provides
an isolated nucleic acid molecule comprising a sequence
of nucleotides substantially as set forth in SEQ ID
NO:14 or a nucleotide sequence having at least 60%
similarity to the nucleotide sequence set forth in SEQ
ID NO:14 or a nucleotide sequence capable of hybridising
15 thereto under low stringency conditions at 42EC and
wherein said nucleotide sequence encodes a novel
haemopoietin receptor or a derivative thereof.

20 In another related embodiment, the present invention
provides an isolated nucleic acid molecule comprising a
sequence of nucleotides substantially as set forth in
SEQ ID NO:16 or a nucleotide sequence having at least
60% similarity to the nucleotide sequence set forth in
SEQ ID NO:16 or a nucleotide sequence capable of
25 hybridising thereto under low stringency conditions at
42EC and wherein said nucleotide sequence encodes a
novel haemopoietin receptor or a derivative thereof.

30 In a further related embodiment, the present invention
provides an isolated nucleic acid molecule comprising a
sequence of nucleotides substantially as set forth in
SEQ ID NO:18 or a nucleotide sequence having at least
60% similarity to the nucleotide sequence set forth in
SEQ ID NO:18 or a nucleotide sequence capable of
35 hybridising thereto under low stringency conditions at
42EC and wherein said nucleotide sequence encodes a
novel haemopoietin receptor or a derivative thereof.

In yet a further related embodiment, the present invention provides an isolated nucleic acid molecule comprising a sequence of nucleotides substantially as set forth in SEQ ID NO:24 or a nucleotide sequence
5 having at least 60% similarity to the nucleotide sequence set forth in SEQ ID NO:24 or a nucleotide sequence capable of hybridising thereto under low stringency conditions at 42EC and wherein said nucleotide sequence encodes a novel haemopoietin
10 receptor or a derivative thereof.

Still yet a further embodiment of the present invention is directed to a sequence of nucleotides substantially as set forth in SEQ ID NO:28 or a nucleotide sequence
15 having at least 60% similarity to the nucleotide sequence set forth in SEQ ID NO:28 or a nucleotide sequence capable of hybridising thereto under low stringency conditions at 42EC and wherein said nucleotide sequence encodes a novel haemopoietin
20 receptor or a derivative thereof.

In still yet another embodiment, the present invention provides an isolated nucleic acid molecule comprising a sequence of nucleotides substantially set forth in SEQ
25 ID NO:38 or a nucleotide sequence having at least 60% similarity to the nucleotide sequence set forth in SEQ ID NO:38 or a nucleotide sequence capable of hybridising thereto under low stringency conditions at 42EC and wherein said nucleotide sequence encodes a novel
30 haemopoietin receptor or a derivative thereof.

The term "receptor" is used in its broadest sense and includes any molecule capable of binding, associating or otherwise interacting with a ligand. Generally, the
35 interaction will have a signalling effect although the present invention is not necessarily so limited. For example, the "receptor" may be in soluble form, often

referred to as a cytokine binding protein. A receptor may be deemed a receptor notwithstanding that its ligand or ligands has or have not been identified.

5 Preferably, the novel receptor is derived from a mammal or a species of bird. Particularly, preferred mammals include humans, primates, laboratory test animals (e.g. mice, rats, rabbits, guinea pigs), livestock animals (e.g. sheep, horses, pigs, cows), companion animals
10 (e.g. dogs, cats) or captive wild animals (e.g. deer, foxes, kangaroos). Although the present invention is exemplified with respect to mice, the scope of the subject invention extends to all animals and in particular humans.

15 The present invention is predicated in part on an ability to identify members of the haemopoietin receptor family with limited sequence similarity. Based on this approach, a genetic sequence has been identified in
20 accordance with the present invention which encodes a novel receptor. The expressed genetic sequence is referred to herein as "NR6". Different forms of NR6 are referred to as, for example, NR6.1, NR6.2 and NR6.3. The nucleotide and corresponding amino acid sequences
25 for these molecules are represented in SEQ ID NOs:12, 14 and 16, respectively.

Preferred human and murine nucleic acid sequences for NR6 or its derivatives include sequences from brain,
30 liver, kidney, neonatal, embryonic, cancer or tumour-derived tissues.

Reference herein to a low stringency at 42EC includes and encompasses from at least about 1% v/v to at least
35 about 15% v/v formamide and from at least about 1M to at least about 2M salt for hybridisation, and at least about 1M to at least about 2M salt for washing

conditions. Alternative stringency conditions may be applied where necessary, such as medium stringency, which includes and encompasses from at least about 16% v/v to at least about 30% v/v formamide and from at least about 0.5M to at least about 0.9M salt for hybridisation, and at least about 0.5M to at least about 0.9M salt for washing conditions, or high stringency, which includes and encompasses from at least about 31% v/v to at least about 50% v/v formamide and from at least about 0.01M to at least about 0.15M salt for hybridisation, and at least about 0.01M to at least about 0.15M salt for washing conditions.

The nucleic acid molecules contemplated by the present invention are generally in isolated form and are preferably cDNA or genomic DNA molecules. In a particularly preferred embodiment, the nucleic acid molecules are in vectors and most preferably expression vectors to enable expression in a suitable host cell. Particularly useful host cells include prokaryotic cells, mammalian cells, yeast cells and insect cells. The cells may also be in the form of a cell line.

Accordingly, another aspect of the present invention provides an expression vector comprising a nucleic acid molecule encoding the novel haemopoietin receptor or a derivative thereof as hereinbefore described, said expression vector capable of expression in a selected host cell.

Another aspect of the present invention contemplates a method for cloning a nucleotide sequence encoding NR6 or a derivative thereof, said method comprising searching a nucleotide data base for a sequence which encodes the amino acid sequence set forth in SEQ ID NO:1, designing one or more oligonucleotide primers based on the nucleotide sequence located in the search, screening a

nucleic acid library with said one or more oligonucleotides and obtaining a clone therefrom which encodes said NR6 or part thereof.

5 Once a novel nucleotide sequence is obtained as indicated above encoding NR6, oligonucleotides may be designed which bind cDNA clones with high stringency. Direct colony hybridisation may be employed or PCR
10 amplification may be used. The use of oligonucleotide primers which bind under conditions of high stringency ensures rapid cloning of a molecule encoding the novel NR6 and less time is required in screening out cloning artefacts. However, depending on the primers used, low or medium stringency conditions may also be employed.

15 Alternatively, a library may be screened directly such as using oligonucleotides set forth in SEQ ID NO:7 or SEQ ID NO:8 or a mixture of both oligonucleotides may be used. In addition, one or more of oligonucleotides
20 defined in SEQ ID NO:2 to 11 may also be used.

Preferably, the nucleic acid library is a cDNA, genomic, cDNA expression or mRNA library.

25 Preferably, the nucleic acid library is a cDNA expression library.

30 Preferably, the nucleotide data base is of human or murine origin and of brain, liver, kidney, neo-natal tissue, embryonic tissue, tumour or cancer tissue origin.

35 Preferred percentage similarities to the reference nucleotide sequences include at least about 70%, more preferably at least about 80%, still more preferably at least about 90% and even more preferably at least about 95% or above.

Another aspect of the present invention provides an isolated nucleic acid molecule comprising a sequence of nucleotides encoding a novel haemopoietin receptor or derivative thereof having an amino acid sequence as set forth in SEQ ID NO:13 or having at least about 50% similarity to all or part thereof.

Still yet another aspect of the present invention provides an isolated nucleic acid molecule comprising a sequence of nucleotides encoding a novel haemopoietin receptor or derivative thereof having an amino acid sequence as set forth in SEQ ID NO:15 or having at least about 50% similarity to all or part thereof.

Even yet another aspect of the present invention provides an isolated nucleic acid molecule comprising a sequence of nucleotides encoding a novel haemopoietin receptor or derivative thereof having an amino acid sequence as set forth in SEQ ID NO:17 or having at least about 50% similarity to all or part thereof.

A further aspect of the present invention provides an isolated nucleic acid molecule comprising a sequence of nucleotides encoding a novel haemopoietin receptor or derivative thereof having an amino acid sequence as set forth in SEQ ID NO:19 or having at least about 50% similarity to all or part thereof.

Even yet a another aspect of the present invention provides an isolated nucleic acid molecule comprising a sequence of nucleotides encoding a novel haemopoietin receptor or derivative thereof having an amino acid sequence as set forth in SEQ ID NO:25 or having at least about 50% similarity to all or part thereof.

Another aspect of the present invention provides an isolated nucleic acid molecule comprising a sequence of

nucleotides encoding a novel haemopoietin receptor or derivative thereof having an amino acid sequence as set forth in one or more of SEQ ID NOs:29 or having at least about 50% similarity to all or part thereof.

5

Preferably, the percentage amino acid similarity is at least about 60%, more preferably at least about 70%, even more preferably at least about 80-85% and still even more preferably at least about 90-95% or greater.

10

The NR6 polypeptide contemplated by the present invention includes, therefore, derivatives which are components, parts, fragments, homologues or analogues of the novel haemopoietin receptors which are preferably encoded by all or part of a nucleotide sequences substantially set forth in SEQ ID NO:12 or 14 or 16 or 18 or 25 or 20 or 24 or 28 or 38 or a molecule having at least about 60% nucleotide similarity to all or part thereof or a molecule capable of hybridising to the nucleotide sequence set forth in SEQ ID NO:12 or 14 or 16 or 18 or 20 or 24 or 28 or 38 or a complementary form thereof. The NR6 molecule may be glycosylated or non-glycosylated. When in glycosylated form, the glycosylation may be substantially the same as naturally occurring haemopoietin receptor or may be a modified form of glycosylation. Altered or differential glycosylation states may or may not affect binding activity of the novel receptor.

30 The NR6 haemopoietin receptor may be in soluble form or may be expressed on a cell surface or conjugated or fused to a solid support or another molecule.

35 As stated above, the present invention further contemplates a range of derivatives of NR6. Derivatives include fragments, parts, portions, mutants, homologues and analogues of the NR6 polypeptide and corresponding

genetic sequence. Derivatives also include single or multiple amino acid substitutions, deletions and/or additions to NR6 or single or multiple nucleotide substitutions, deletions and/or additions to the genetic sequence encoding NR6. "Additions" to amino acid sequences or nucleotide sequences include fusions with other peptides, polypeptides or proteins or fusions to nucleotide sequences. Reference herein to ANR6" includes reference to all derivatives thereof including functional derivatives or NR6 immunologically interactive derivatives.

Analogues of NR6 contemplated herein include, but are not limited to, modification to side chains, incorporating of unnatural amino acids and/or their derivatives during peptide, polypeptide or protein synthesis and the use of crosslinkers and other methods which impose conformational constraints on the proteinaceous molecule or their analogues.

Examples of side chain modifications contemplated by the present invention include modifications of amino groups such as by reductive alkylation by reaction with an aldehyde followed by reduction with NaBH_4 ; amidination with methylacetimidate; acylation with acetic anhydride; carbamoylation of amino groups with cyanate; trinitrobenzylation of amino groups with 2, 4, 6-trinitrobenzene sulphonic acid (TNBS); acylation of amino groups with succinic anhydride and tetrahydrophthalic anhydride; and pyridoxylation of lysine with pyridoxal-5-phosphate followed by reduction with NaBH_4 .

The guanidine group of arginine residues may be modified by the formation of heterocyclic condensation products with reagents such as 2,3-butanedione, phenylglyoxal and glyoxal.

The carboxyl group may be modified by carbodiimide activation via O-acylisourea formation followed by subsequent derivitisation, for example, to a corresponding amide.

5

Sulphydryl groups may be modified by methods such as carboxymethylation with iodoacetic acid or iodoacetamide; performic acid oxidation to cysteic acid; formation of a mixed disulphides with other thiol
10 compounds; reaction with maleimide, maleic anhydride or other substituted maleimide; formation of mercurial derivatives using 4-chloromercuribenzoate, 4-chloromercuriphenylsulphonic acid, phenylmercury chloride, 2-chloromercuri-4-nitrophenol and other
15 mercurials; carbamoylation with cyanate at alkaline pH.

Tryptophan residues may be modified by, for example, oxidation with N-bromosuccinimide or alkylation of the indole ring with 2-hydroxy-5-nitrobenzyl bromide or
20 sulphenyl halides. Tyrosine residues on the other hand, may be altered by nitration with tetranitromethane to form a 3-nitrotyrosine derivative.

Modification of the imidazole ring of a histidine
25 residue may be accomplished by alkylation with iodoacetic acid derivatives or N-carbethoxylation with diethylpyrocarbonate.

Examples of incorporating unnatural amino acids and
30 derivatives during peptide synthesis include, but are not limited to, use of norleucine, 4-amino butyric acid, 4-amino-3-hydroxy-5-phenylpentanoic acid, 6-aminohexanoic acid, t-butylglycine, norvaline, phenylglycine, ornithine, sarcosine, 4-amino-3-hydroxy-
35 6-methylheptanoic acid, 2-thienyl alanine and/or D-isomers of amino acids. A list of unnatural amino acid, contemplated herein is shown in Table 1.

These types of modifications may be important to stabilise NR6 if administered to an individual or for use as a diagnostic reagent.

- 5 Crosslinkers can be used, for example, to stabilise 3D conformations, using homo-bifunctional crosslinkers such as the bifunctional imido esters having $(CH_2)_n$ spacer groups with $n=1$ to $n=6$, glutaraldehyde, N-hydroxysuccinimide esters and hetero-bifunctional
- 10 reagents which usually contain an amino-reactive moiety such as N-hydroxysuccinimide and another group specific-reactive moiety such as maleimido or dithio moiety (SH) or carbodiimide (COOH). In addition, peptides can be conformationally constrained by, for example,
- 15 incorporation of C" and N "-methylamino acids, introduction of double bonds between C_α and C_β atoms of amino acids and the formation of cyclic peptides or analogues by introducing covalent bonds such as forming an amide bond between the N and C termini, between two
- 20 side chains or between a side chain and the N or C terminus.

TABLE 1

	Non-conventional amino acid	Code	Non-conventional amino acid	Code
5	aminobutyric acid	Abu	L-N-methylalanine	Nmala
	Amino-"-methylbutyrate	Mgabu	L-N-methylarginine	Nmarg
	aminocyclopropane-	Cpro	L-N-methylasparagine	Nmasn
	carboxylate		L-N-methylaspartic acid	Nmasp
10	aminoisobutyric acid	Aib	L-N-methylcysteine	Nmcys
	aminonorbornyl-	Norb	L-N-methylglutamine	Nmgln
	carboxylate		L-N-methylglutamic acid	Nmglu
	cyclohexylalanine		ChexaL-N-methylhistidine	Nmhis
	cyclopentylalanine	Cpen	L-N-methylisoleucine	Nmile
15	D-alanine	Dal	L-N-methylleucine	Nmleu
	D-arginine	Darg	L-N-methyllysine	Nmlys
	D-aspartic acid	Dasp	L-N-methylmethionine	Nmmet
	D-cysteine	Dcys	L-N-methylnorleucine	Nmnle
	D-glutamine	Dgln	L-N-methylnorvaline	Nmnva
20	D-glutamic acid	Dglu	L-N-methylornithine	Nmorn
	D-histidine	Dhis	L-N-methylphenylalanine	Nmphe
	D-isoleucine	Dile	L-N-methylproline	Nmpro
	D-leucine	Dleu	L-N-methylserine	Nmser
	D-lysine	Dlys	L-N-methylthreonine	Nmthr
25	D-methionine	Dmet	L-N-methyltryptophan	Nmtrp
	D-ornithine	Dorn	L-N-methyltyrosine	Nmtyr
	D-phenylalanine	Dphe	L-N-methylvaline	Nmval
	D-proline	Dpro	L-N-methylethylglycine	Nmetg
	D-serine	Dser	L-N-methyl-t-butylglycine	Nmtbug
30	D-threonine	Dthr	L-norleucine	Nle
	D-tryptophan	Dtrp	L-norvaline	Nva
	D-tyrosine	Dtyr	"-methyl-aminoisobutyrate	Maib
	D-valine	Dval	"-methyl-(-aminobutyrate	Mgabu
	D-"-methylalanine	Dmala	"-methylcyclohexylalanine	Mchexa
35	D-"-methylarginine	Dmarg	"-methylcyclopentylalanine	Mcpen
	D-"-methylasparagine	Dmasn	"-methyl-"-naphthylalanine	Manap
	D-"-methylaspartate	Dmasp	"-methylpenicillamine	Mpen

	D--methylcysteine	Dmcys	N-(4-aminobutyl)glycine	Nglu
	D--methylglutamine	Dmgln	N-(2-aminoethyl)glycine	Naeg
	D--methylhistidine	Dmhis	N-(3-aminopropyl)glycine	Norn
	D--methylisoleucine	Dmile	N-amino--methylbutyrate	Nmaabu
5	D--methylleucine	Dmleu	--naphthylalanine	Anap
	D--methyllysine	Dmlys	N-benzylglycine	Nphe
	D--methylmethionine	Dmmet	N-(2-carbamylethyl)glycine	Nglu
	D--methylornithine	Dmorn	N-(carbamylmethyl)glycine	Nasn
	D--methylphenylalanine	Dmphe	N-(2-carboxyethyl)glycine	Nglu
10	D--methylproline	Dmpro	N-(carboxymethyl)glycine	Nasp
	D--methylserine	Dmser	N-cyclobutylglycine	Ncbut
	D--methylthreonine	Dmthr	N-cycloheptylglycine	Nchep
	D--methyltryptophan	Dmtrp	N-cyclohexylglycine	Nchex
	D--methyltyrosine	Dmty	N-cyclodecylglycine	Ncdec
15	D--methylvaline	Dmval	N-cylcododecylglycine	Ncdod
	D-N-methylalanine	Dnmala	N-cyclooctylglycine	Ncoct
	D-N-methylarginine	Dnmarg	N-cyclopropylglycine	Ncpro
	D-N-methylasparagine	Dnmasn	N-cycloundecylglycine	Ncund
	D-N-methylaspartate	Dnmasp	N-(2,2-diphenylethyl)glycine	Nbhm
20	D-N-methylcysteine	Dnmcys	N-(3,3-diphenylpropyl)glycine	Nbhe
	D-N-methylglutamine	Dnmgln	N-(3-guanidinopropyl)glycine	Narg
	D-N-methylglutamate	Dnmglu	N-(1-hydroxyethyl)glycine	Nthr
	D-N-methylhistidine	Dnmhis	N-(hydroxyethyl)glycine	Nser
	D-N-methylisoleucine	Dnmile	N-(imidazolylethyl)glycine	Nhis
25	D-N-methylleucine	Dnmleu	N-(3-indolylyethyl)glycine	Nhtrp
	D-N-methyllysine	Dnmlys	N-methyl-(-aminobutyrate	Nmgabu
	N-methylcyclohexylalanine	Nmchexa	D-N-methylmethionine	Dnmmet
	D-N-methylornithine	Dnmorn	N-methylcyclopentylalanine	
	Nmcpenn-methylglycine	Nala	D-N-methylphenylalanine	Dnmphe
30	N-methylaminoisobutyrate	Nmaib	D-N-methylproline	Dnmpro
	N-(1-methylpropyl)glycine	Nile	D-N-methylserine	Dnmser
	N-(2-methylpropyl)glycine	Nleu	D-N-methylthreonine	Dnmthr
	D-N-methyltryptophan	Dnmtrp	N-(1-methylethyl)glycine	Nval
	D-N-methyltyrosine	Dnmtyr	N-methyla-naphthylalanine	Nmanap
35	D-N-methylvaline	Dnmval	N-methylpenicillamine	Nmpen
	(-aminobutyric acid	Gabu	N-(p-hydroxyphenyl)glycine	Nhtyr
	L-t-butylglycine	Tbug	N-(thiomethyl)glycine	Ncys

	L-ethylglycine	Etg	penicillamine	Pen
	L-homophenylalanine	Hphe	L--methylalanine	Mala
	L--methylarginine	Marg	L--methylasparagine	Masn
	L--methylaspartate	Masp	L--methyl-t-butylglycine	Mtbug
5	L--methylcysteine	Mcys	L-methylethylglycine	Metg
	L--methylglutamine	Mgln	L--methylglutamate	Mglu
	L--methylhistidine	Mhis	L--methylhomophenylalanine	Mhphe
	L--methylisoleucine	Mile	N-(2-methylthioethyl)glycine	Nmet
	L--methyllleucine	Mleu	L--methyllysine	Mlys
10	L--methylmethionine	Mmet	L--methylnorleucine	Mnle
	L--methylnorvaline	Mnva	L--methylornithine	Morn
	L--methylphenylalanine	Mphe	L--methylproline	Mpro
	L--methylserine	Mser	L--methylthreonine	Mthr
	L--methyltryptophan	Mtrp	L--methyltyrosine	Mtyr
15	L--methylvaline	Mval	L-N-methylhomophenylalanine	Nmhph
	N-(N-(2,2-diphenylethyl) carbamylmethyl)glycine	Nnbhm	N-(N-(3,3-diphenylpropyl) carbamylmethyl)glycine	Nnbhe
	1-carboxy-1-(2,2-diphenyl-	Nmbc	ethylamino)cyclopropane	

20

The present invention further contemplates chemical analogues of NR6 capable of acting as antagonists or agonists of NR6 or which can act as functional analogues of NR6. Chemical analogues may not necessarily be derived from NR6 but may share certain conformational similarities. Alternatively, chemical analogues may be specifically designed to mimic certain physiochemical properties of NR6. Chemical analogues may be chemically synthesised or may be detected following, for example, natural product screening.

30

The identification of NR6 permits the generation of a range of therapeutic molecules capable of modulating expression of NR6 or modulating the activity of NR6. Modulators contemplated by the present invention includes agonists and antagonists of NR6 expression. Antagonists of NR6 expression include antisense

35

molecules, ribozymes and co-suppression molecules. Agonists include molecules which increase promoter ability or interfere with negative regulatory mechanisms. Agonists of NR6 include molecules which
5 overcome any negative regulatory mechanism. Antagonists of NR6 include antibodies and inhibitor peptide fragments.

10 Other derivatives contemplated by the present invention include a range of glycosylation variants from a completely unglycosylated molecule to a modified glycosylated molecule. Altered glycosylation patterns may result from expression of recombinant molecules in different host cells.

15 Another embodiment of the present invention contemplates a method for modulating expression of NR6 in a subject such as a human or mouse, said method comprising contacting the genetic sequence encoding NR6
20 with an effective amount of a modulator of NR6 expression for a time and under conditions sufficient to up-regulate or down-regulate or otherwise modulate expression of NR6. Modulating NR6 expression provides a means of modulating NR6-ligand interaction or NR6
25 stimulation of cell activities.

Another aspect of the present invention contemplates a method of modulating activity of NR6 in a human, said method comprising administering to said mammal a
30 modulating effective amount of a molecule for a time and under conditions sufficient to increase or decrease NR6 activity. The molecule may be a proteinaceous molecule or a chemical entity and may also be a derivative of NR6 or its ligand or a chemical analogue or truncation
35 mutant of NR6 or its ligand.

The present invention, therefore, contemplates a

pharmaceutical composition comprising NR6 or a derivative thereof or a modulator of NR6 expression or NR6 activity and one or more pharmaceutically acceptable carriers and/or diluents. These components are referred to as the active ingredients.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions (where water soluble) and sterile powders for the extemporaneous preparation of sterile injectable solutions. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dilution medium comprising, for example, water, ethanol, polyol (for example, glycerol, propylene glycol and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of surfactants. The preventions of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze-drying

technique which yield a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

- 5 When the active ingredients are suitably protected they may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsule, or it may be compressed into tablets, or it may be
- 10 incorporated directly with the food of the diet. For oral therapeutic administration, the active compound may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like.
- 15 Such compositions and preparations should contain at least 1% by weight of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 5 to about 80% of the weight of the unit. The amount of active
- 20 compound in such therapeutically useful compositions in such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 0.1 ug and 2000 mg of active
- 25 compound. Alternative dosage amounts include from about 1 Fg to about 1000 mg and from about 10 Fg to about 500 mg.

- 30 The tablets, troches, pills, capsules and the like may also contain the components as listed hereafter: A binder such as gum, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as
- 35 magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavouring agent such as peppermint, oil of wintergreen,

or cherry flavouring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, 5 tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavouring 10 such as cherry or orange flavour. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compound(s) may be incorporated into sustained-release 15 preparations and formulations.

The present invention also extends to forms suitable for topical application such as creams, lotions and gels as well as a range of "paints" which are applied to skin 20 and through which the active ingredients are absorbed.

Pharmaceutically acceptable carriers and/or diluents include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic 25 and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art and except insofar as any conventional media or agent is incompatible with the active ingredient, their use in the therapeutic 30 compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

It is especially advantageous to formulate parenteral 35 compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units

suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the novel dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active material for the treatment of disease in living subjects having a diseased condition in which bodily health is impaired as herein disclosed in detail.

The principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as hereinbefore disclosed. A unit dosage form can, for example, contain the principal active compound in amounts ranging from 0.5 :g to about 2000 mg. Expressed in proportions, the active compound is generally present in from about 0.5 :g to about 2000 mg/ml of carrier. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients.

Dosages may also be expressed per body weight of the recipient. For example, from about 10 ng to about 1000 mg/kg body weight, from about 100 ng to about 500 mg/kg body weight and for about 1 Fg to above 250 mg/kg body weight may be administered.

The pharmaceutical composition may also comprise genetic molecules such as a vector capable of transfecting target cells where the vector carries a nucleic acid molecule capable of modulating NR6 expression or NR6

activity. The vector may, for example, be a viral vector.

5 Still another aspect of the present invention is directed to antibodies to NR6 and its derivatives. Such antibodies may be monoclonal or polyclonal and may be selected from naturally occurring antibodies to NR6 or may be specifically raised to NR6 or derivatives thereof. In the case of the latter, NR6 or its
10 derivatives may first need to be associated with a carrier molecule. The antibodies and/or recombinant NR6 or its derivatives of the present invention are particularly useful as therapeutic or diagnostic agents. For example, NR6 antibodies or antibodies to its ligand
15 may act as antagonists.

For example, NR6 and its derivatives can be used to screen for naturally occurring antibodies to NR6. These may occur, for example in some autoimmune diseases.
20 Alternatively, specific antibodies can be used to screen for NR6. Techniques for such assays are well known in the art and include, for example, sandwich assays and ELISA. Knowledge of NR6 levels may be important for diagnosis of certain cancers or a predisposition to
25 cancers or for monitoring certain therapeutic protocols.

Antibodies to NR6 of the present invention may be monoclonal or polyclonal. Alternatively, fragments of antibodies may be used such as Fab fragments.
30 Furthermore, the present invention extends to recombinant and synthetic antibodies and to antibody hybrids. A "synthetic antibody" is considered herein to include fragments and hybrids of antibodies. The antibodies of this aspect of the present invention are
35 particularly useful for immunotherapy and may also be used as a diagnostic tool for assessing apoptosis or monitoring the program of a therapeutic regimen.

For example, specific antibodies can be used to screen for NR6 proteins. The latter would be important, for example, as a means for screening for levels of NR6 in a cell extract or other biological fluid or purifying NR6 made by recombinant means from culture supernatant fluid. Techniques for the assays contemplated herein are known in the art and include, for example, sandwich assays and ELISA.

10 It is within the scope of this invention to include any second antibodies (monoclonal, polyclonal or fragments of antibodies or synthetic antibodies) directed to the first mentioned antibodies discussed above. Both the first and second antibodies may be used in detection
15 assays or a first antibody may be used with a commercially available anti-immunoglobulin antibody. An antibody as contemplated herein includes any antibody specific to any region of NR6.

20 Both polyclonal and monoclonal antibodies are obtainable by immunization with the enzyme or protein and either type is utilizable for immunoassays. The methods of obtaining both types of sera are well known in the art. Polyclonal sera are less preferred but are relatively
25 easily prepared by injection of a suitable laboratory animal with an effective amount of NR6, or antigenic parts thereof, collecting serum from the animal, and isolating specific sera by any of the known immunoabsorbent techniques. Although antibodies
30 produced by this method are utilizable in virtually any type of immunoassay, they are generally less favoured because of the potential heterogeneity of the product.

35 The use of monoclonal antibodies in an immunoassay is particularly preferred because of the ability to produce them in large quantities and the homogeneity of the product. The preparation of hybridoma cell lines for

monoclonal antibody production derived by fusing an
immortal cell line and lymphocytes sensitized against
the immunogenic preparation can be done by techniques
which are well known to those who are skilled in the
5 art.

Another aspect of the present invention contemplates a
method for detecting NR6 in a biological sample from a
subject said method comprising contacting said
10 biological sample with an antibody specific for NR6 or
its derivatives or homologues for a time and under
conditions sufficient for an antibody-NR6 complex to
form, and then detecting said complex.
The presence of NR6 may be accomplished in a number of
15 ways such as by Western blotting and ELISA procedures.
A wide range of immunoassay techniques are available as
can be seen by reference to US Patent Nos. 4,016,043, 4,
424,279 and 4,018,653. These, of course, includes both
single-site and two-site or "sandwich" assays of the
20 non-competitive types, as well as in the traditional
competitive binding assays. These assays also include
direct binding of a labelled antibody to a target.

Sandwich assays are among the most useful and commonly
25 used assays and are favoured for use in the present
invention. A number of variations of the sandwich assay
technique exist, and all are intended to be encompassed
by the present invention. Briefly, in a typical forward
assay, an unlabelled antibody is immobilized on a solid
30 substrate and the sample to be tested brought into
contact with the bound molecule. After a suitable
period of incubation, for a period of time sufficient to
allow formation of an antibody-antigen complex, a second
antibody specific to the antigen, labelled with a
35 reporter molecule capable of producing a detectable
signal is then added and incubated, allowing time
sufficient for the formation of another complex of

antibody-antigen-labelled antibody. Any unreacted material is washed away, and the presence of the antigen is determined by observation of a signal produced by the reporter molecule. The results may either be

5 qualitative, by simple observation of the visible signal, or may be quantitated by comparing with a control sample containing known amounts of hapten. Variations on the forward assay include a simultaneous assay, in which both sample and labelled antibody are

10 added simultaneously to the bound antibody. These techniques are well known to those skilled in the art, including any minor variations as will be readily apparent. In accordance with the present invention, the sample is one which might contain NR6 including cell

15 extract, tissue biopsy or possibly serum, saliva, mucosal secretions, lymph, tissue fluid and respiratory fluid. The sample is, therefore, generally a biological sample comprising biological fluid but also extends to fermentation fluid and supernatant fluid such as from a

20 cell culture.

In the typical forward sandwich assay, a first antibody having specificity for the NR6 or antigenic parts thereof, is either covalently or passively bound to a

25 solid surface. The solid surface is typically glass or a polymer, the most commonly used polymers being cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene. The solid supports may be in the form of tubes, beads, discs of microplates, or any

30 other surface suitable for conducting an immunoassay. The binding processes are well-known in the art and generally consist of cross-linking covalently binding or physically adsorbing, the polymer-antibody complex is washed in preparation for the test sample. An aliquot

35 of the sample to be tested is then added to the solid phase complex and incubated for a period of time sufficient (e.g. 2-40 minutes or overnight if more

convenient) and under suitable conditions (e.g. from about room temperature to about 37°C) to allow binding of any subunit present in the antibody. Following the incubation period, the antibody subunit solid phase is washed and dried and incubated with a second antibody specific for a portion of the hapten. The second antibody is linked to a reporter molecule which is used to indicate the binding of the second antibody to the hapten.

10

An alternative method involves immobilizing the target molecules in the biological sample and then exposing the immobilized target to specific antibody which may or may not be labelled with a reporter molecule. Depending on the amount of target and the strength of the reporter molecule signal, a bound target may be detectable by direct labelling with the antibody. Alternatively, a second labelled antibody, specific to the first antibody is exposed to the target-first antibody complex to form a target-first antibody-second antibody tertiary complex. The complex is detected by the signal emitted by the reporter molecule.

15

In another alternative method, the NR6 ligand is immobilised to a solid support and a biological sample containing NR6 brought into contact with its immobilised ligand. Binding between NR5 and its ligand can then be determined using an antibody to NR6 which itself may be labelled with a reporter molecule or a further anti-immunoglobulin antibody labelled with a reporter molecule could be used to detect antibody bound to NR6.

20

By "reporter molecule" as used in the present specification, is meant a molecule which, by its chemical nature, provides an analytically identifiable signal which allows the detection of antigen-bound antibody. Detection may be either qualitative or

25

quantitative. The most commonly used reporter molecules in this type of assay are either enzymes, fluorophores or radionuclide containing molecules (i.e. radioisotopes) and chemiluminescent molecules.

5 In the case of an enzyme immunoassay, an enzyme is conjugated to the second antibody, generally by means of glutaraldehyde or periodate. As will be readily recognized, however, a wide variety of different conjugation techniques exist, which are readily
10 available to the skilled artisan. Commonly used enzymes include horseradish peroxidase, glucose oxidase, beta-galactosidase and alkaline phosphatase, amongst others. The substrates to be used with the specific enzymes are generally chosen for the production, upon hydrolysis by
15 the corresponding enzyme, of a detectable colour change. Examples of suitable enzymes include alkaline phosphatase and peroxidase. It is also possible to employ fluorogenic substrates, which yield a fluorescent product rather than the chromogenic substrates noted
20 above. In all cases, the enzyme-labelled antibody is added to the first antibody hapten complex, allowed to bind, and then the excess reagent is washed away. A solution containing the appropriate substrate is then added to the complex of antibody-antigen-antibody. The
25 substrate will react with the enzyme linked to the second antibody, giving a qualitative visual signal, which may be further quantitated, usually spectrophotometrically, to give an indication of the amount of hapten which was present in the sample.
30 "Reporter molecule" also extends to use of cell agglutination or inhibition of agglutination such as red blood cells on latex beads, and the like.

Alternately, fluorescent compounds, such as fluorescein
35 and rhodamine, may be chemically coupled to antibodies without altering their binding capacity. When activated by illumination with light of a particular wavelength,

the fluorochrome-labelled antibody adsorbs the light energy, inducing a state to excitability in the molecule, followed by emission of the light at a characteristic colour visually detectable with a light microscope. As in the EIA, the fluorescent labelled antibody is allowed to bind to the first antibody-hapten complex. After washing off the unbound reagent, the remaining tertiary complex is then exposed to the light of the appropriate wavelength the fluorescence observed indicates the presence of the hapten of interest. Immunofluorescence and EIA techniques are both very well established in the art and are particularly preferred for the present method. However, other reporter molecules, such as radioisotope, chemiluminescent or bioluminescent molecules, may also be employed.

The present invention also contemplates genetic assays such as involving PCR analysis to detect the NR6 gene or its derivatives. Alternative methods or methods used in conjunction include direct nucleotide sequencing or mutation scanning such as single stranded conformational polymorphisms analysis (SSCP) as specific oligonucleotide hybridisation, as methods such as direct protein truncation tests.

The nucleic acid molecules of the present invention may be DNA or RNA. When the nucleic acid molecule is in a DNA form, it may be genomic DNA or cDNA. RNA forms of the nucleic acid molecules of the present invention are generally mRNA.

Although the nucleic acid molecules of the present invention are generally in isolated form, they may be integrated into or ligated to or otherwise fused or associated with other genetic molecules such as vector molecules and in particular expression vector molecules. Vectors and expression vectors are generally capable of

replication and, if applicable, expression in one or both of a prokaryotic cell or a eukaryotic cell. Preferably, prokaryotic cells include *E. coli*, *Bacillus* *sp* and *Pseudomonas* *sp*. Preferred eukaryotic cells
5 include yeast, fungal, mammalian and insect cells.

Accordingly, another aspect of the present invention contemplates a genetic construct comprising a vector portion and a mammalian and more particularly a human
10 NR6 gene portion, which NR6 gene portion is capable of encoding an NR6 polypeptide or a functional or immunologically interactive derivative thereof.

Preferably, the NR6 gene portion of the genetic
15 construct is operably linked to a promoter on the vector such that said promoter is capable of directing expression of said NR6 gene portion in an appropriate cell.

20 In addition, the NR6 gene portion of the genetic construct may comprise all or part of the gene fused to another genetic sequence such as a nucleotide sequence encoding maltose binding protein or glutathione-S-transferase or part thereof.

25 The present invention extends to such genetic constructs and to prokaryotic or eukaryotic cells comprising same.

The present invention also extends to any or all
30 derivatives of NR6 including mutants, part, fragments, portions, homologues and analogues or their encoding genetic sequence including single or multiple nucleotide or amino acid substitutions, additions and/or deletions to the naturally occurring nucleotide or amino acid
35 sequence.

NR6 may be important for the proliferation,

differentiation and survival of a diverse array of cell types. Accordingly, it is proposed that NR6 or its functional derivatives be used to regulate development, maintenance or regeneration in an array of different
5 cells and tissues *in vitro* and *in vivo*. For example, NR6 is contemplated to be useful in modulating neuronal proliferation, differentiation and survival.

Soluble NR6 polypeptides are also contemplated to be
10 useful in the treatment of a range of diseases, injuries or abnormalities.

Membrane bound or soluble NR6 may be used *in vitro* on nerve cells or tissues to modulate proliferation,
15 differentiation or survival, for example, in grafting procedures or transplantation.

As stated above, the NR6 of the present invention or its functional derivatives may be provided in a
20 pharmaceutical composition comprising the NR6 together with one or more pharmaceutically acceptable carriers and/or diluents. In addition, the present invention contemplates a method of treatment comprising the administration of an effective amount of a NR6 of the
25 present invention. The present invention also extends to antagonists and agonists of NR6s and their use in therapeutic compositions and methodologies.

A further aspect of the present invention contemplates
30 the use of NR6 or its functional derivatives in the manufacture of a medicament for the treatment of NR6 mediated conditions defective or deficient.

Still a further aspect of the present invention
35 contemplates a ligand for NR6 preferably, in isolated or recombinant form or a derivative of said ligand.

The present invention further contemplates knockout animals such as mice or other murine species for the NR6 gene including homozygous and heterozygous knockout animals. Such animals provide a particularly useful
5 live in vivo model for studying the effects of NR6 as well as screening for agents capable of acting as agonists or antagonists of NR6.

According to this embodiment there is provided a
10 transgenic animal comprising a mutation in at least one allele of the gene encoding NR6. Additionally, the present invention provides a transgenic animal comprising a mutation in two alleles of the gene encoding NR6. Preferably, the transgenic animal is a
15 murine animal such as a mouse or rat.

The present invention is further described by the following non-limiting Figures and Examples.

20 In the Figures:

Figure 1 is a diagrammatic representation showing expansion of sequenced region of the mouse NR6 gene indicating splicing patterns seen in the three forms of
25 NR6 cDNA, NR6.1, NR6.2 and NR6.3.

Figure 2 is a representation of the nucleotide sequence of the mouse NR6 gene, containing exons encoding the cDNA from nucleotide 148 encoding D50 of the cDNAs shown
30 in SEQ ID NOs:12 and 14 to the end of the 3N untranslated region shared by both NR6.1, NR6.2 and NR6.3. In this figure, this region encompasses nucleotides g1182 to g6617. This sequence is also defined in SEQ ID NO:28.

35

Figure 3 is a representation of the nucleotide sequence of the mouse genomic NR6 gene with additional 5N

sequences. The coding exons of NR6 span approximately 11kb of the mouse genome. There are 9 coding exons separated by 8 introns:

	exon1	at least 239nt	intron1	5195nt
5	exon 2	282nt	intron2	214nt
	exon3	130nt	intron3	107nt
	exon4	170nt	intron4	1372nt
	exon5	158nt	intron5	68nt
	exon6	169nt	intron6	2020nt
10	exon6	188nt	intron7	104nt
	exon8	43nt	intron8	181nt
	exon9	252nt		

Exon 1 encoding the signal sequence, exon 2 the Ig-like domain, exons 3 to 6 the hemopoietin domain. Exons 7, 8 and 9 are alternatively spliced.

Figure 4 is a diagrammatic representation showing the genomic structure of murine NR-6.

Figure 5 is a diagrammatic representation showing targetting of the NR6 locus by homologous recombination.

Single and three letter abbreviations for amino acid residues used in the specification are summarised in Table 2:

5

TABLE 2

	Amino Acid	Three-letter Abbreviation	One-letter Symbol
10	Alanine	Ala	A
	Arginine	Arg	R
	Asparagine	Asn	N
	Aspartic acid	Asp	D
	Cysteine	Cys	C
15	Glutamine	Gln	Q
	Glutamic acid	Glu	E
	Glycine	Gly	G
	Histidine	His	H
	Isoleucine	Ile	I
20	Leucine	Leu	L
	Lysine	Lys	K
	Methionine	Met	M
	Phenylalanine	Phe	F
	Proline	Pro	P
25	Serine	Ser	S
	Threonine	Thr	T
	Tryptophan	Trp	W
	Tyrosine	Tyr	Y
	Valine	Val	V
30	Any residue	Xaa	X

TABLE 3
SUMMARY OF SEQ ID NO.

	Sequence	SEQ ID NO.
5	Amino acid sequence WSXWS	1
	Oligonucleotide primers and probes listed in Example 1	2-11
	Nucleotide sequence of NR6.1 ¹	12
	Amino acid sequence of NR6.1	13
10	Nucleotide sequence of NR6.2 ²	14
	Amino acid sequence of NR6.2	15
	Nucleotide sequence of NR6.3 ³	16
	Amino acid sequence of NR6.3	17
	Nucleotide sequence of products generated by 5N RACE of brain cDNA using NR6 specific primers ⁴	18
	Amino acid sequence of SEQ ID NO:18	19
	Nucleotide sequence unique to 5N RACE of brain cDNA	20
20	Amino acid sequence for SEQ ID NO:20	21
	Unspliced murine NR6 nucleotide sequence	22
	PCR product for human NR6	23
	Nucleotide sequence of clone HFK-66 encoding human NR6	24
25	Amino acid sequence of SEQ ID NO:24	25
	Oligonucleotide sequences UP1 and LP1, respectively	26-27
	Genomic nucleotide sequence of murine NR6	28
	Amino acid sequence of SEQ ID NO:28	29
30	Murine NR6.1 oligonucleotide primers	30, 31
	Murine IL-3 signal sequence	32
	Linker sequence for mouse IL-3 signal sequence and FLAG epitope	33-35
	Genomic nucleotide sequence of murine NR6 containing additional 5N sequence	38
35	Oligonucleotide 2199 and 2200, respectively	36, 37
	N-terminal region of NR6	39

¹The polyadenylation signal AATAAATAAA is at nucleotide position 1451 to 1460; NR6.1 (SEQ ID NO:12) and NR6.2 (SEQ ID NO:14) are identical to nucleotide 1223 encoding Q407, the represents the end of an exon. NR6.1 splices out an exon present only in NR6.2 and uses a different reading frame for the final exon which is shared with NR6.2; this corresponds to amino acids VLPACL at amino acid residue positions 408-413. The region of 3N-untranslated DNA shared by NR6.1, NR6.2 and NR6.3 is from nucleotide 1240 to 1475. The WSXWS motif is at amino acid residues 330 to 334.

²The polyadenylation signal AATAAA is at nucleotide positions 1494 to 1503. The WSXWS motif is at amino acid residues 330 to 334. NR6.1 and NR6.2 are identical to nucleotide 1223 encoding Q407 which represents the end of an exon. NR6.2 splices in an exon beginning at amino acid residue D408, nucleotide 1224 and ends at residue G422, nucleotide 1264. The region of 3N-untranslated DNA shared by NR6.1, NR6.2 and NR6.3 is from nucleotide position 1283 to 1517.

³The nucleotide and amino acid numbering corresponds to SEQ ID NO:12 and 14. The WSXWS motif is at amino acid residues 330 to 334. The polyadenylation signal AATAAATAAA is from nucleotide 1781 to 1780. NR6.1, NR6.2 and NR6.3 are identical to nucleotide 1223 encoding Q407, this represents the end of an exon. NR6.3 fails to splice from this position and, therefore, translation continues through the intron, giving rise to the C-terminal protein region from amino acid residues 408 to 461. The region of 3N untranslated DNA shared by NR6.1, NR6.2 and NR6.3 is from nucleotide 1469 to 1804.

⁴The nucleotide sequence is identical to NR6.1, NR6.2 and NR6.3 from nucleotide C151, the first nucleotide for Pro51. The numbering from this nucleotide is the same

as for SEQ ID NO:14 and 16. The 5N of this point is unique to the products generated by 5N RACE not being found in NR6.1, NR6.2 and NR6.3 and is represented in SEQ ID NOs:20 and 21.

5

⁵Structure of the murine genomic NR6 locus. The coding exons of NR6 span approximately 11kb of the mouse genome. There are 9 coding exons separated by 8 introns:

10

exon 1 at least 239nt	intron1 5195nt
exon 2 282nt	intron2 214nt
exon 3 130nt	intron3 107nt
exon 4 170nt	intron 4 1372nt
exon 5 158nt	intron5 68nt
exon 6 169nt	intron6 2020nt
exon 7 188nt	intron7 104nt
exon 8 43nt	intron8 181nt
exon 9 252nt	

20

Exon 1 encodes the signal sequence, exon 2 the Ig-like domain, exons 3 to 6 the hemopoietin domain. Exons 7, 8 and 9 are alternatively spliced.

25 The NRG molecules of the present invention have a range of utilities referred to in the subject specification. Additional utilities include:

1. Identification of molecules that interact with NR6.

30 These may include :

a) a corresponding ligand using standard orphan receptor techniques (26),

35 b) monoclonal antibodies that act either as receptors antagonists or agonists,

- c) mimetic or antagonistic peptides isolated using phage display technology (27,28),
- d) small molecule natural products that act either as antagonists or agonists.

2. Development of diagnostics to detect deletions/rearrangements in the NR6 gene.

The NR6 knock-out mice studies described herein provide a useful model for this utility. There are also applications in the field of reproduction. For example, people can be tested for their NR6 status. NR6 +/- carriers might be expected to give rise to offspring with developmental problems.

EXAMPLE 1
Oligonucleotides

M116: 5' ACTCGCTCCAGATTCCCGCCTTTT 3' [SEQ ID NO:2]
 5 M108: 5' TCCCGCCTTTTTCGACCCATAGAT 3' [SEQ ID NO:3]
 M159: 5' GGTACTTGGCTTGGAAGAGGAAAT 3' [SEQ ID NO:4]
 M242: 5' CGGCTCACGTGCACGTCGGGTGGG 3' [SEQ ID NO:5]
 M112: 5' AGCTGCTGTAAAGGGCTTCTC 3' [SEQ ID NO:6]
 WSDWS 5' (A/G) CTCCA (A/G) TC (A/G) CTCCA 3' [SEQ ID NO:7]
 10 WSEWS 5' (A/G) CTCCA (C/T) TC (A/G) CTCCA 3' [SEQ ID NO:8]
 1944 5' AAGTGTGACCATCATGTGGAC 3' [SEQ ID NO:9]
 2106 5' GGAGGTGTTAAGGAGGCG 3' [SEQ ID NO:10]
 2120 5' ATGCCCGCGGGTCGCCCCG 3' [SEQ ID NO:11]

15

EXAMPLE 2

Isolation of initial NR6 cDNA clones using oligonucleotides designed against the conserved WSXWS motif found in members of the haemopoietin receptor family

20

(i) A commercial adult mouse testis cDNA library cloned into the UNI-ZAP bacteriophage (Stratagene, CA, USA; Catalogue numbers 937 308) was used to infect *Escherichia coli* of the strain LE392. Infected bacteria
 25 were grown on twenty 150 mm agar plates, to give approximately 50,000 plaques per plate. Plaques were then transferred to duplicate 150 mm diameter nylon membranes (Colony/Plaque Screen, NEN Research Products, MA, USA), bacteria were lysed and the DNA was denatured
 30 and fixed by autoclaving at 100°C for 1 min with dry exhaust. The filters were rinsed twice in 0.1% (w/v) sodium dodecyl sulfate (SDS), 0.1 x SSC (SSC is 150 mM sodium chloride, 15 mM sodium citrate dihydrate) at room temperature and pre-hybridized overnight at 42°C in 6 x
 35 SSC containing 2 mg/ml bovine serum albumin, 2 mg/ml Ficoll, 2 mg/ml polyvinylpyrrolidone, 100 mM ATP, 10 mg/ml tRNA, 2 mM sodium pyrophosphate, 2 mg/ml salmon

sperm DNA, 0.1% (w/v) SDS and 200 mg/ml sodium azide. The pre-hybridisation buffer was removed. 1.2 Fg of the degenerate oligonucleotides for hybridization (WSDWS; Example 1) were phosphorylated with T4 polynucleotide kinase using 960 mCi of $\gamma^{32}\text{P}$ -ATP (Bresatec, S.A., Australia). Unincorporated ATP was separated from the labelled oligonucleotide using a pre-packed gel filtration column (NAP-5; Pharmacia, Uppsala, Sweden). Filters were hybridized overnight at 42°C in 80 ml of the prehybridisation buffer containing 0.1% (w/v) SDS, rather than NP40, and 10^6 - 10^7 cpm/ml of labelled oligonucleotide. Filters were briefly rinsed twice at room temperature in 6 x SSC, 0.1% (v/v) SDS, twice for 30 min at 45°C in a shaking waterbath containing 1.5 l of the same buffer and then briefly in 6 x SSC at room temperature. Filters were then blotted dry and exposed to autoradiographic film at -70°C using intensifying screens, for 7 - 14 days prior to development. Plaques that appeared positive on orientated duplicate filters were picked, eluted in 1 ml of 100 mM NaCl, 10 mM MgCl_2 , 10 mM Tris.HCl pH7.4 containing 0.5% (w/v) gelatin and 0.5% (v/v) chloroform and stored at 4°C. After 2 days LE392 cells were infected with the eluate from the primary plugs and replated for the secondary screen. This process was repeated until hybridizing plaques were pure.

Once purified, positive cDNAs were excised from the ZAP II bacteriophage according to the manufacturer's instructions (Stratagene, CA, USA) and cloned into the plasmid pBluescript. A CsCl purified preparation of the DNA was made and this was sequenced on both strands. Sequencing was performed using an Applied Biosystems automated DNA sequencer, with fluorescent dideoxynucleotide analogues according to the manufacturer's instructions. The DNA sequence was analysed using software supplied by Applied Biosystems.

Two clones isolated from the mouse testis cDNA library shared large regions of nucleotide sequence identity 68-1 and 68-2 and appeared to encode a novel member of the haemopoietin receptor family and the inventors gave the putative receptor the working name "NR6".

(ii) In a parallel series of experiments, a commercial mouse brain cDNA library (STRATAGENE #967319, Balb/c day-20, whole brain cDNA/Uni-ZAP XR Vector) was used to infect *E. coli* strain XL1-Blue MRF=. Infected bacteria were grown on 90x135mm square agar plates to give about 25,000 plaques per plate. Plaques were then transferred to positively charged nylon membranes, Hybond-N(+) (Amersham RPN 203B), bacteria were lysed and the DNA was denatured with denaturing 0.5 M NaOH, 1.5 M NaCl at room temperature for 7 min. The membranes were neutralized with 0.5 M Tris-HCL pH7.2, 1.5 M NaCl, 1 mM EDTA at room temperature for 10 min before the DNA fixation by UV crosslinking.

A mixture of WSDWS and WSEWS oligonucleotide probes (SEQ ID NOs: 7 and 8) were labelled with a [32 P]-ATP (TOYOBO #PNK-104 Kination kit). The membranes from the mouse brain cDNA library were then hybridized with the mixture of WSDWS and WSEWS oligonucleotide probes in the Rapid Hybridization Buffer (Amersham, RPN1636) at 42°C for 16 hours. Filters were washed with 1xSSC/0.1% (w/v) SDS at 42°C before autoradiography. Plaques that appeared positive on orientated duplicate filters were picked and replated on *E. coli*, XL1-Blue MRFN with the process of immobilisation on nylon membranes, hybridization of membranes with oligonucleotide probes, washing and autoradiography repeated until pure plaques had been obtained.

The cDNA fragment from pure positively hybridizing plaques was isolated by excision with the helper phage

- strain ExAssist according to the manufacturer's instructions (Stratagene, #967319). Sequencing was performed after the amplification with Ampli-Taq DNA polymerase and Taq dideoxy terminator cycle sequencing kit (Perkin Elmer, #401150) by 25 cycles of 96°C for 10 sec, 50°C for 5 sec, 60°C for 4 min followed by 60°C for 5 min with the sequencing primers on an ABI model 377 DNA sequencer.
- 10 One clone, MBC-8, from the mouse brain library shared large regions of nucleotide sequence identity with both the 68-1 and 68-2 clones isolated from the mouse testis cDNA library.
- 15 (iii) In a third series of experiments, total RNA was prepared from the mouse osteoblastic cell line, KUSA, according to the method of Chirgwin et al. (15), and poly(A)+RNA was further purified by oligo(dT)-cellulose chromatography (Pharmacia Biotech). Complementary DNA
- 20 was synthesized by oligo(dT) priming, inserted into the UniZAP XR directional cloning vector (Stratagene), and packaged into 8 phage using Gigapack Gold (Stratagene), yielding 1.25×10^7 independent clones.
- 25 Approximately 10^6 clones were screened essentially as described in (ii) above. Briefly, probes were labeled with ^{32}P using T4 polynucleotide kinase and prehybridization was performed for 4 hr in the Rapid hybridization buffer (Amersham LIFE SCIENCE) at 42°C.
- 30 Filters (Hybond N+, Amersham) were then hybridized for 19 hr under the same condition with the addition of ^{32}P -labeled WSXWS mix oligonucleotides and washed 3 times. The final wash was for 30 min in 1 x SSPE, 0.1% (w/v) SDS at 42°C. Filters were then exposed with an
- 35 intensifying screen to Kodak X-OMAT AR film for 5 days.

Isolated clones were subjected to the *in vivo* excision

of pBluescript SK(-) phagemid (Stratagene), and plasmid DNA was prepared by the standard method. DNA sequences were determined using an ABI PRISM 377 DNA Sequencer (Perkin Elmer) with appropriate synthetic
5 oligonucleotide primers. A clone pKUSA166 shared large regions of nucleotide sequence identity with the MBC-8, 68-1 and 68-2 clones isolated from the mouse brain and testis cDNA libraries.

10

EXAMPLE 3

Isolation of further NR6 cDNA clones using probes specific for NR6

(i) In order to identify other cDNA libraries
15 containing cDNA clones for NR6, the inventors performed PCR upon 1 μ l aliquots of λ -bacteriophage cDNA libraries made from mRNA from various human tissues and using oligonucleotides 2070 and 2057, designed from the sequence of 68-1 and 68-2, as primers. Reactions
20 contained 5 μ l of 10 x concentrated PCR buffer (Boehringer Mannheim GmbH, Mannheim, Germany), 1 μ l of 10 mM dATP, dCTP, dGTP and dTTP, 2.5 μ l of the oligonucleotides HYB2 and either T3 or T7 at a concentration of 100 mg/ml, 0.5 μ l of Taq polymerase
25 (Boehringer Mannheim GmbH) and water to a final volume of 50 μ l. PCR was carried out in a Perkin-Elmer 9600 by heating the reactions to 96°C for 2 min and then for 25 cycles at 96°C for 30 sec, 55°C for 30 sec and 72°C for 2 min. PCR products were resolved on an agarose gel,
30 immobilized on a nylon membrane and hybridized with ³²P-labelled oligonucleotide 1943 (SEQ ID NO:42).

In addition to the original library, a mouse brain cDNA library appeared to contain NR6 cDNAs. These were
35 screened using a ³²P-labelled oligonucleotides 1944, 2106, 2120 (Example 1) or with a fragment of the original NR6 cDNA clone from 68-1 (nucleotide 934 to the

end of NR6.1 in Figure 1) labelled with ^{32}P using a random decanucleotide labelling kit (Bresatec). Conditions used were similar to those described in (i) above except that for the labelled oligonucleotides, filters were washed at 55°C rather than 45°C , while for the NR6 cDNA fragment prehybridization and hybridization was carried out in $2\times\text{SSC}$ and filters were washed at $0.2\times\text{SSC}$ at 65°C . Again, as described in (i) above, positively hybridising plaques were purified, the cDNAs were recovered and cloned into plasmids pBluescript II or pUC19. Independent cDNA clones were sequenced on both strands.

Using this procedure, 6 further clones, 68-5, 68-35, 68-41, 68-51, 68-77 and 73-23, contained large regions of sequence identity with 68-1, 68-2, MBC-8 and pKUSA166.

In a parallel series of experiments, further screening was performed with hybridization probes prepared from the 1.7 kbp EcoRI-XhoI fragment excised from pKUSA166. This fragment was excised and labeled with ^{32}P by using T7QuickPrime Kit (Pharmacia Biotech). Approximately 6×10^5 clones were screened. Hybond N+ filters (Amersham) were first prehybridized for 4hr at 42°C in 50% (v/v) formamide, $5\times\text{SSPE}$, $5\times\text{Denhardt's}$ solution, 0.1% (w/v) SDS, and 0.1mg/ml denatured salmon sperm DNA. Hybridization was for 16 hours under the same conditions with the addition of ^{32}P -labelled NR6- cDNA fragment probes. Finally the filters were washed once for 1hr in $0.2\times\text{SSC}$, 0.1% (w/v) SDS at 68°C . Eight clones were isolated, and phage clones were subjected to the *in vivo* excision of the pBluescript SK(-) phagemid (Stratagene). The plasmid DNAs were prepared by the standard method. DNA sequences were determined by an ABI PRISM 377 DNA Sequencer using appropriate synthetic oligonucleotide primers.

Using this procedure 8 further clones from the KUSA library contained large regions of sequence identity with 68-1, 68-2, MBC-8, pKUSA166, 68-5, 68-35, 68-41, 68-51, 68-77 and 73-23 were isolated.

5

EXAMPLE 4**Isolation of genomic DNA encoding NR6**

DNA encoding the murine NR6 genomic locus was also isolated using the 68-1 cDNA as a probe. Two positive clones, 2-2 and 57-3, were isolated from a mouse 129/Sv strain genomic DNA library cloned into λ FIX. These clones were overlapping and the position of the restriction sites, introns and exons were determined in the conventional manner. The region of the genomic clones containing exons and the intervening introns were sequenced on both strands using an Applied Biosystems automated DNA sequencer, with fluorescent dideoxynucleotide analogues according to the manufacturer's instructions. Figure 2 shows the nucleotide sequence and corresponding amino acid sequence of the translation regions. This is also shown in SEQ ID NOs:30 and 31. Figure 3 provides the genomic NR6 gene sequence but with additional 5N sequence. This is also represented in SEQ ID NO:38 in relation to this sequence. The coding exons of NR6 span approximately 11kb of the mouse genome. There are 9 coding exons separated by 8 introns:

30	exon1	at least 239nt	intron1	5195nt
	exon2	282nt	intron2	214nt
	exon3	130nt	intron3	107nt
	exon4	170nt	intron4	1372nt
	exon5	158nt	intron5	68nt
35	exon6	169nt	intron6	2020nt
	exon7	188nt	intron7	104nt
	exon8	43nt	intron8	181nt

exon9 252nt

Exon 1 encodes the signal sequence, exon 2 the Ig-like domain, exons 3 to 6 the hemopoietin domain. Exons 7, 8 and 9 are alternatively spliced.

EXAMPLE 5

5N RACE analysis of NR6

5'-RACE was used to investigate the nature of the sequence 5' of nucleotide 960, encoding Ile321 of NR6.1, 2 and 3. The nucleotide and corresponding amino acid sequences are shown in SEQ ID NOs:12, 14 and 16, respectively. 5'-RACE was performed using Advantage KlenTaq polymerase (CLONTECH, CAT NO. K1905-1) on mouse brain Marathon-ready cDNA (CLONTECH, CAT NO. 7450-1) according to the manufacturer's instructions. Briefly, the first rounds of amplification were performed using 5µl of cDNA in a total volume of 50µl, with 1mM each of the primers AP1&M116 [SEQ ID NO:2] or AP1&M159 [SEQ ID NO:4] by 35 cycles of 94°C x 0.5min, 68°C x 2.0min on GeneAmp 2400 (Perkin-Elmer). An amount of 5µl of 50-fold diluted product from the first amplification was then re-amplified ; for the products generated with primers AP1 and M116 [SEQ ID NO:2] in the first amplification, 1 mM of the primers AP2&M108 [SEQ ID NO:3] were used in the second amplification. For the products generated with primers AP1 and M116 [SEQ ID NO:2] in the first amplification, two separate secondary reactions were performed, one reaction with 1 mM primers AP2&M242 [SEQ ID NO:5] and the other with 1 mM primers AP2&M112 [SEQ ID NO:6]. Amplification was achieved using 25 cycles of 94°C x 0.5min, 68°C x 2.0min. These samples were analyzed by agarose gel electrophoresis. When a single ethidium bromide staining amplification

product was observed, it was purified by QIAquick PCR purification kit according to the manufacturer's instructions (QIAGEN, CAT NO. DG-0281) and its sequence was directly determined using both primers used in the secondary amplification step, that is AP2 and either M108 [SEQ ID NO:3], M242 [SEQ ID NO:5] or M112 [SEQ ID NO:6].

EXAMPLE 6

10

Cloning of NR6

From the initial screens of mouse brain and testis cDNA libraries with the degenerate WSXWS oligonucleotides and subsequent screening of cDNA libraries from mouse testis, mouse brain and the KUSA osteoblastic cells line a total of 18 NR6 cDNAs have been isolated. Nucleotide sequence of NR6 was also determined from 5'RACE analysis of brain cDNA. Additionally, two murine genomic DNA clones encoding NR6 have also been isolated.

20

Comparison of the NR6 cDNA clones revealed a common region of nucleotide sequence which included a 123 base pairs 5'-untranslated region and 1221 base pairs open reading frame, stretching from the putative initiation methionine, Met1 to Gln407 (SEQ ID NOs:12, 14 and 16, respectively). Within this common open reading frame, a haemopoietin receptor domain was observed which contained the four conserved cysteine residues and the five amino acid motif WSXWS typical of members of the haemopoietin receptor family, was observed.

30

Further analyses revealed that after nucleotide 1221, three different classes of NR6 cDNAs could be found, these were termed NR6.1, NR6.2 and NR6.3 (SEQ ID NOs:12, 14 and 16, respectively). Each encoded a receptor that appeared to lack a classical transmembrane domain and, would, therefore be likely to be secreted into the

35

extracellular environment. Although the putative C-terminal region of the three classes of NR6 proteins appear to be different, the cDNAs encoding them also had a common region of 3'-untranslated region.

5

With regard to SEQ ID NOs:12, 14 and 16, the number of both nucleotides and amino acids begins at the putative initiation methionine. NR6.1 and NR6.2 are identical to nucleotide 1223 encoding Q407, this represents the end of an exon. NR6.1 splices out an exon present only in NR6.2 and uses a different reading frame for the final exon which is shared with NR6.2. The 3N-untranslated region is shared by NR6.1, NR6.2 and NR6.3, NR6.2 splices in an exon starting with nucleotide 1224 encoding D408 and ending with nucleotide 1264 encoding the first nucleotide in the codon for G422 and uses a different reading frame for the final exon which is shared with NR6.2 (see Figure 1). NR6.3 fails to splice from position nucleotide 1224, therefore, translation continues through the intron, giving rise to the C-terminal protein region.

25

The sequence of NR6 cDNA products generated by 5'-RACE amplification from mouse brain cDNA preparation is shown in SEQ ID NO:18. The nucleotide sequence identified using 5'-RACE appeared to be identical to the sequence of cDNAs encoding NR6.1, NR6.2, and NR6.3 from nucleotide C151, the first nucleotide for the codon for Pro51. 5' of this nucleotide, the sequences diverged and the sequence is unique not being found in NR6.1, NR6.2 or NR6.3. Additionally, there is a single nucleotide difference, with the sequence from the RACE containing an G rather than an A at nucleotide 475, resulting in Thr159 becoming Ala.

35

Analysis of the genomic clones, revealed that they were overlapping and contained exons encoding the majority of

the coding region of the three forms of NR6 (Figures 1, 2 and 3). These genomic clones, contained exons encoding from Asp50 (nucleotide 148) of the NR6 cDNAs. Sequence 5' of this in the cDNAs, including the 5'-
5 untranslated region and the region encoding Met1 to Gln49 (SEQ ID NOs:12, 14 and 16), and the 5' end predicted from analysis of 5' RACE products (SEQ ID NO:18) were not present in the two genomic clones isolated.

10

Analysis of the NR6 genomic DNA clones also provided an explanation of the three classes of NR6 cDNAs found. It is likely that NR6.1, NR6.2 and NR6.3 arise through alternative splicing of NR6 mRNA (Figure 1). The last
15 amino acid residue that these different NR6 proteins are predicted to share is Gln407. SEQ ID NO:18 shows that Gln407 is the last amino acid encoded by the exon that covers nucleotides g5850 to g6037 (see Figure 2). Alternative splicing from the end of this exon (Figure
20 1) accounts for the generation of cDNAs encoding NR6.1 (SEQ ID NO:12), NR6.2 (SEQ ID NO:14) and NR6.3 (SEQ ID NO:16). In the case of NR6.1, the region from g6038 to g6425 is spliced out, leading to juxtaposition of g6037 and g6426. In the case of NR6.2, the region from g6038
25 to 6141 is spliced out, an exon from 6142 to g6183 is retained and then this is followed by splicing out of the region from g6183 to g6425. NR6.3 appears to arise when there is no splicing from nucleotide g6038. For
30 all three forms, a secreted rather than transmembrane form is generated, these differ however in their predicted C-terminal region. The genomic NR6 sequence with additional 5N sequence is shown in Figure 3.

EXAMPLE 7

35

ESTs

Databases were searched with the murine NR6

corresponding to the unspliced version shown in SEQ ID NO:16. The murine NR6 sequence used is shown in SEQ ID NO:22.

The databases searched were:

5

- (i) dbEST - Database of Expressed Sequence Tags
National Center for Biotechnology Information National
Library of Medicine, 38A, 8N8058600 Rockville Pike,
Bethesda, MD 20894 Phone: 0011-1-301-496-2475 Fax:
10 0015-1-301-480-9241 USA.
- (ii) DNA Data Bank of Japan DNA Database Release 3689.
Prepared by: Sanzo Miyazawa Manager/Database
Administrator Hidenori Hayashida Scientific Reviewer
15 Yukiko Yamazaki/Eriko Hatada/Hiroaki Serizawa
Annotators/reviewers Motono Horie/Shigeko Suzuki/Yumiko
Satao Secretaries/typists DNA Data Bank of Japan National
Institute of Genetics Center for Genetic Information
research Laboratory of Genetic Information Analyses 1111
20 Yata Mishima, Shizuoka 411 Japan.

(iii) EMBL Nucleic Acid Sequence Data Bank Release
47.0.

25 (iv) EMBL Nucleic Acid Sequence Data Bank Weekly Updates
Since Release 44.

(v) Genetic Sequence Data Bank NCBI-GenBank Release 94
National Center for Biotechnology Information National
30 Library of Medicine, 38A, 8N805 8600 Rockville Pike,
Bethesda, MD 20894 Phone: 0011-1-301-495-2475 Fax:
0015-1-301-480-9241 USA.

(vi) Cumulative Updates since NCBI-GenBank Release 88
35 National Center for Biotechnology Information National
Library of Medicine, 38A, 8N805 8600 Rockville Pike,
Bethesda, MD 20894 USA.

The search of the databases with the murine probe identified several EST's having sequence similarity to the probe. The EST's were:

- 5 W66776 (murine sequence)
- MM5839 (murine sequence)
- AA014965 (murine sequence)
- W46604 (human sequence)
- W46603 (human sequence)
- 10 H14009 (human sequence)
- N78873 (human sequence)
- R87407 (human sequence).

EXAMPLE 8

15 Isolation of 3N cDNA clones encoding human NR6

PCR products encoding human NR6 were generated using oligonucleotides UP1 and LP1 (see below) based on human ESTs (Genbank Acc:H14009, Genbank Acc:AA042914) that
20 were identified from databases searched with murine NR6 sequence (SEQ ID NO:22). PCR was performed on a human fetal liver cDNA library (Marathon ready cDNA CLONTECH #7403-1) using Advantage Klen Tag Polymerase mix (CLONTECH #8417-1) in the buffer supplied at 941C for
25 30s and 681C for 3 min for 35 cycles followed by 681C for 4 min and then stopping at 151C. A standard PCR programme for the Perkin-Elmer GeneAmp PCT system 2400 thermal cycle was used. The PCR yielded a prominent product of approximately 560 base pairs (bp; SEQ ID
30 NO:18), which was radiolabelled with ["-³²P] dCTP using a random priming method (Amersham, RPN, 1607, Mega prime kit) and used to screen a human fetal kidney 5N-STRETCH PLUS cDNA library (CLONTECH #HL1150x). Library screens were performed using Rapid Hybridisation Buffer
35 (Amersham, RPN 1636) according to manufacturer's instructions and membranes washed at 651C for 30 min in 0.1xSSC/0.1% (w/v) SDS. Two independent cDNA clones

were obtained as lambda phage and subsequently subcloned and sequenced. Both clones (HFK-63 and HFK-66) contained 1.4 kilobase (kb) inserts that showed sequence similarity with murine NR6. The sequence and
5 corresponding amino acid translation of HFK-66 is shown in SEQ ID NO:24.

The translation protein sequences of clone HFK-66 shows a high degree of sequence similarity with the mouse NR6.
10

OLIGONUCLEOTIDES

UP1: 5NTCC AGG CAG CGG TCG GGG GAC AAC 3N [SEQ ID NO:26]
LP1: 5N TTG CTC ACA TCG TCC ACC ACC TTC 3N [SEQ ID
NO:27]

15

EXAMPLE 9

Genomic Structure of Human NR6

Human genomic DNA clones encoding human NR6 was
20 isolated by screening a human genomic library (Lambda
FIXJII Stratagene 946203) with radiolabelled
oligonucleotides, 2199 and 2200 (see below). These
oligonucleotides were designed based on human ESTs
(Genbank Acc:R87407, Genbank Acc:H14009) that were
25 identified from databases searched with murine NR6.
Filters were hybridised overnight at 37°C in 6xSSC
containing 2 mg/ml bovine serum albumin, 2 mg/ml Ficoll,
2mg/ml polyvinylpyrrolidone, 100 mM ATP, 10 mg/ml tRNA,
2 mM sodium pyrophosphate, 2 mg/ml salmon sperm DNA,
30 0.1% (w/v) SDS and 200 mg/ml sodium azide and washed at
65°C in 6 x SSC/0.1% SDS. Five independent genomic
clones were obtained and sequenced. The extend of
sequence obtained has determined that the clones overlap
and exhibit a similar genomic structure to murine NR6.
35 Exon coding regions are almost identical over the region
covered by the genomic clones while intron coding
regions differ, although the size of the introns are

comparable. The extent of known overlap is shown in Fig. 5.

OLIGONUCLEOTIDES:

5

2199: 5N CCC ACG CTT CTC ATC GGA TTC TCC CTG 3N [SEQ ID NO:36]

2200: 5N CAG TCC ACA CTG TCC TCC ACT CGG TAG 3N [SEQ ID NO:37]

10

EXAMPLE 10

Northern Blot Analysis of Human NR6 mRNA Expression

15 Clontech Multiple Tissue Northern Blots (Human MTN Blot, CLONTECH #7760-1, Human MTN Blot IV, CLONTECH #7766-I, Human Brain MTN Blot II, CLONTECH #7755-1, Human Brain MTN Blot III, CLONTECH #7750) were probed with a radiolabelled 3N human NR6 cDNA clone, HFK-66 (SEQ ID NO:24). The clone was labelled with ["-³²P] dCTP using a random priming method (Amersham, RPN 1607, Mega prime kit). Hybridisation was performed in Express Hybridisation Solution (CLONTECH H50910) for 3 hours at 67°C and membranes were washed in 0.1xSSC/0.1% w/v SDS at 50°C.

20 A 1.8 kb transcript was detected in a variety of human tissues encompassing reproductive, digestive and neural tissues. High levels were observed in the heart, placenta, skeletal muscle, prostate and various areas of the brain, lower levels were observed in the testis, uterus, small intestine and colon. Photographs showing these Northern blots are available upon request. This expression pattern differs from the expression pattern observed with murine NR6.

35

EXAMPLE 11

Mouse NR6 Expression Vectors

pEF-FLAG/mNR6.1

5 The mature coding region of mouse NR6.1 was amplified using the PCR to introduce an in-frame Asc I restriction enzyme site at the 5' end of the mature coding region and an Mlu I site at the 3' end, using the following oligonucleotides:-

10

5N oligo 5N-AGCTGGCGCGCCTCCCGGGCGGATCGGGAGCCCAC-3N [SEQ ID NO:30]

3N oligo 5N-AGCTACGCGTTTAGAGTTTAGCCGGCAG-3N[SEQ ID NO:31]

15

The resulting PCR derived DNA fragment was then digested with Asc I and Mlu I and cloned into the Mlu I site of pEF-FLAG. Expression of NR6 is under the control of the polypeptide chain elongation factor 1 α promoter as described (16) and results in the secretion, using the IL3 signal sequence from pEF-FLAG, of N-terminal FLAG-tagged NR6 protein.

20

pEF-FLAG was generated by modifying the expression vector pEF-BOS as follows:-

25

pEF-BOS (16) was digested with Xba I and a linker was synthesized that encoded the mouse IL3 signal sequence (MVLASSTTSIH TMLLLLLMLFHLGLQASIS) and the FLAG epitope (DYKDDDDK). Asc I and Mlu I restriction enzyme sites were also introduced as cloning sites. The sequence of the linker is as follows:-

30

35 M M V L A S S T T S I H T
CTAGACTAGTGCTGACACAATGGTTCTTGCCAGCTCTACCACCAGCATCCACACCA
TG

TGATCACGACTGTGTTACCAAGAACGGTCGAGATGGTGGTCGTAGGTGTGGTAC

5 L L L L L M L F H L G L Q A S I S Asc
I
CTGCTCCTGCTCCTGATGCTCTTCCACCTGGGACTCCAAGCTTCAATCTCGGCGCG
CC
GACGAGGACGAGGACTAGCAGAAGGTGGACCCTGAGGTTCTGAAGTTAGAGCCGCGC
GG

10 D Y K D D D D K Mlu I
AGGACTACAAGGACGACGATGACAAGACGCGTGCTAGCACTAGT

15 TCCTGATGTTCTGCTGCTACTGTTCTGCGCACGATCGTGATCAGATC

The two oligonucleotides were annealed together and
ligated into the Xba I site of pEF-BOS to give pEF-FLAG.

20 pCOS1/FLAG/mNR6 & pCH01/FLAG/mNR6

A DNA fragment containing the sequences encoding IL3
signal sequence/Flag/mNR6 and the poly(A) adenylation
signal from human G-CSF cDNA, was excised from pEF-
FLAG/mNR6 using the restriction enzyme *EcoR* I. This DNA
25 fragment was then inserted into the *EcoR* I cloning site
of pCOS1 and pCH01

The pCOS1 and pCH01 vectors were constructed as follows.
pCH01 is also described in reference (17) but with a
30 different selectable marker.

pCOS1 was prepared by digesting HEF-12h-g"1 (see Figure
24 of International Patent Publication No. WO 92/19759)
with *EcoRI* and *SmaI* and ligating the digesting product
35 iwht an *EcoRI*-*NotI*-*BamHI* adaptor (Takara 4510). The
resulting plasmid comprises an *EFI*" promoter/enhancer,
Nco^r marker gene, SV40E, ori and an *Amp*^r marker gene.

pCH01 was constructed by digesting DHFR-PMh-gr1 (see Figure 25 of International Patent Publication No. WO 92/19759) with PvuI and Eco47III and ligating same with pCOSI digested with PvuI and Eco47III. The resulting vector, pCH01, comprises an EFI" promoter/enhancer, an DHFR marker gene, SV40E, Ori and a Amp^r gene.

EXAMPLE 12

mRN6 has been expressed as an NN Flag tagged protein following transfection of CHO cells and as a CN Flag tagged protein following transfection of KUSA cells in both cases varying levels of dimeric and aggregated NR6 were secreted.

EXAMPLE 13

Murine NR6 expression

NR6 expression studies were conducted in murine Northern Blots. At the level of sensitivity used in the adult mouse, NR6 expression was detected in salivary gland, lung and testis. During embryonic development, NR6 is expressed in fetal tissues from day 10 of gestation through to birth. In cell lines, NR6 expression has been observed in the T-lymphoid line CTLL-2 as well as in FD-PyMT (FDC-P1 myeloid cells expressing polyoma midle T gene), and fibroblastoid cells including bone marrow and fetal liver stromal lines.

EXAMPLE 14

Expression, purification and characterisation of CHO and KUSA mNR6

The methods provide for the production of a dimeric form of CHO derived NN FLAG-mNR6 without refolding. All

other methods are capable of producing NR6 and are encompassed by the present invention.

A. Production of CHO derived N' FLAG-mNR6 (dimeric form)

(i) Protein Production

To analyse structure and functional activity, a cDNA fragment containing the entire coding sequence of murine NR6 with an N-terminal FLAG (NN FLAG) sequence was cloned into the EcoRI site of the expression vector pCHO1. For stable production of N-terminal FLAG-tagged NR6 the vector contains the DHFR (dihydrofolate reductase) gene as a selective marker with the NR6 gene under the control of an EF1a promoter. CHO cells were transfected with the construct using a polycationic liposome transfection reagent (Lipofectamine, GibcoBRL).

(ii) Lipofectamine transfection method

Using six well tissue culture plates either 2×10^5 KUSA cells in 2ml IMDM + 10% (v/v) FCS or 2×10^5 CHO cells were cultured in 2ml "-MEM + 10% (v/v) FCS until 70% confluent. 2Fg DNA diluted in 100Fl OPTI-MEM I (Gibco BRL, USA) was mixed gently with 12Fl lipofectamine diluted in 100Fl OPTI-MEM I and incubated at room temperature for 30min to allow DNA complex formation. DNA complexes were gently diluted in a total volume of 1ml of OPTI-MEM I and overlaid onto washed KUSA or CHO cell monolayers. A further 1ml IMDM + 20% (v/v) FCS (KUSA cells) or 1ml "-MEM + 20% (v/v) FCS (CHO cells) was added to transfected cells after 5 hours. At 24 hours, the culture medium was replaced with fresh complete growth medium. At 48 hours after transfection, selection was applied. A methotrexate resistant clone secreting comparatively high levels of NR6 was selected and expanded for further analysis.

(iii) Protein expression

CHO cells were grown to confluence in roller bottles in nucleoside free "-MEM + 10% (v/v) FCS. Selection was maintained by using 100 ng/ml Methotrexate in the conditioned media according to manufacturer instructions. Expression was monitored by Biosensor and harvesting found to be optimal at 3 to 4 days.

10 B. Protein Analysis

(i) Biosensor analysis

Expression and purification was monitored by Biosensor analysis (BiaCore™, Sweden) where anti FLAG peptide M2 antibody (Kodak Eastman, USA), specific for the FLAG peptide sequence was bound to the sensorchip. Fractions were analysed for binding to the sensor surface (resonance units) and the sample then removed from the surface using 50 mM Diethylamine pH 12.0 prior to analysis of the next fraction. Immobilisation and running conditions of the Biosensor follow the manufacturer's instructions.

25 (ii) Protein Production

In order to generate and characterise NR6, conditioned media (2 L) produced by CHO cells was harvested after day 3, post confluence. Conditioned media was concentrated using diafiltration with a 10,000 molecular weight cut-off. (Easy flow, Sartorius, Aus). At a volume of 200 ml (i.e. 10 x concentrated) the sample was buffer exchanged into 20 mM Tris, 0.15M NaCl, 0.02% (v/v) Tween 20 pH 7.5 (Buffer A).

35

(iii) Immunoprecipitation and Western Blot analysis of mNR6

Concentrated conditioned media (1ml) was immunoprecipitated with M2 affinity resin (20Fl, Kodak Eastman). To examine the structural characterisation of mNR6 SDS PAGE was performed under reducing and non-reducing conditions. Separation was performed on NOVEX 4-20% (v/v) Tris/glycine gradient gels and protein transferred on PVDF membrane. Western blots were probed with biotinylated M2 antibody (primary, 1:500) and then streptavidin peroxidase (secondary, 1:3000). Samples were visualised by autoradiography using electrochemiluminescence (ECL, Dupont, USA).

By regression analysis of prestained standards (BIORAD, Aus.) the molecular weight of the monomeric unit was calculated to be 65,000 daltons. Under non-reducing conditions the molecular weight was calculated to be 127,000 indicating that NR6 is a disulphide linked dimer. A tetrameric complex running at approximately 250,000 daltons was also observed. Although a band running at approximately 50,000 daltons was observed, no monomeric NR6 was detected under non-reducing conditions indicating that the majority of NR6 expressed in this system is disulphide linked.

(iv) Affinity Chromatography of mNR6

Concentrated conditioned media (200 ml) was applied to M2 affinity resin (5ml) under gravity. To enhance recovery the unbound fraction was reapplied to the column four times prior to extensive washing of the column with 200 volumes of Buffer A. Biosensor analysis indicates that approximately 20% of the M2 binding originally present in the concentrate remains in the unbound fraction. The bound fraction was eluted from the column using an immunodesorbant (50 ml); actisept (Sterogene Labs, USA).

(v) Ion exchange and Desalting of mNR6

In order to buffer exchange mNR6 prior to anion chromatography, 10 ml batches of the eluted fraction (50 ml) were applied to an XK column (400 x 26 mm I.D.) containing G25 sepharose (Pharmacia, Sweden). Chromatography was developed at 4 ml/min using an FPLC (Pharmacia, Sweden) equipped with an online UV280 and conductivity monitor. The mobile phase was 10 mM Tris, 0.1M NaCl, 0.02% v/v Tween, pH 8.0. 10 ml fractions were collected between 12.5 min and 25 min to optimise recovery and removal of salt. Fractions were analysed by Biosensor analysis and pooled according to binding.

All pooled active fractions were diluted with an equal volume of 20 mM Tris, 0.02% (v/v) Tween, pH 8.5 (Buffer B) and then loaded onto a Mono Q 5/5 (Pharmacia, Sweden) at a flow rate of 2 ml/min. The column was washed with buffer B. Elution was performed using a linear gradient between buffer B and buffer B containing 0.6M NaCl over 30 min at a flow rate of 1 ml/min. Fractions (1 minute) were collected and analysed on the Biosensor and also by SDS PAGE and Western blot analysis. Fractions 15 to 26 (approximately 0.4M NaCl) appear to contain the majority of mNR6 as indicated by the Biosensor.

C. Production of CHO derived N' FLAG-mNR6 (monomeric form)

(i) Protein Production

A cDNA fragment containing the entire coding sequence of murine NR6 with an N-terminal FLAGJ sequence was cloned into the expression vector pCHO1 for production of N-terminal FLAG-tagged protein. This vector contains a neomycin resistance gene with expression of the NR6 gene under the control of an EF1" promoter. This expression

construct was transfected into CHO cells using Lipofectamine (Gibco BRL, USA) according to the manufacturer instructions. Transfected cells were cultured in IMDM + 10% (v/v) FCS with resistant cells selected in geneticin (600Fg/ml, Gibco BRL, USA). A neomycin resistant clone, secreting comparatively high levels of NR6 was selected and expanded for further analysis.

10 (ii) Protein expression

N' FLAG-NR6 expressed in serum free conditioned media (10 litre) was harvested from transfected CHO and cells. Collected media was concentrated using a CH2 ultrafiltration system equipped with a SLY10 cartridge (Amicon molecular weight cut-off 10,000). Preliminary examination of the expressed product under reducing and non-reducing SDS PAGE followed by western blot analysis was performed. Visualisation of the protein on Westerns was specific to the primary antibody anti FLAG M2. Under reducing conditions a band approximately at 65,000 daltons was observed. Under non-reducing conditions, dimer and larger molecular weight aggregates were observed. These are disulphide linked monomers as they are not present in the reducing gel. Small amounts of monomer appear to be present in non-reducing gels.

25 (iii) Affinity Chromatography of NR6

Concentrated conditioned media was applied to an anti FLAG M2 affinity resin (100 x 16 mm I.D.). After washing the unbound proteins off the column, the bound proteins were eluted using FLAG peptide (60Fg/ml) in PBS.

35 (iv) Ion Exchange Chromatography of NR6

Eluted fractions from affinity column were dialysed overnight against 20 mM Tris-HCl pH 8.5 (buffer C)

containing 50 mM Dithiothreitol (DTT) using 25,000 cut-off dialysis tubing (Spectra/Por7, Spectrum). The dialysed fractions were loaded onto Mono Q 5/5 (Pharmacia, Sweden) previously equilibrated with buffer C containing 5 mM DTT. Chromatography was developed using a linear gradient between buffer C and buffer C containing 1.0 M NaCl at a flow rate of 0.5 ml / min.

(v) Refolding of NR6

Fractions containing NR6 from the Mono Q were adjusted to 50 mM DTT and left overnight at 41C. To initiated refolding the sample was then dialysed against 50 mM Tris-HCl (pH 8.5), 2 M Urea, 0.1% (v/v) Tween 20, 10 mM Glutathione (reduced) and 2 mM Glutathione (oxidised) at a final protein concentration of 100 Fg / ml. Folding was carried out at ambient temperature with one change of the buffer over 24 hours.

(v) Reversed Phase High Performance Liquid Chromatography (RP-HPLC)

The folded product was further purified by RP-HPLC using a Vydac C4 resin (250 x 4.6 mm I.D.) previously equilibrated with 0.1% (v/v) Trifluoroacetic acid (TFA). Elution was carried out using a linear gradient from 0 to 80% (v/v) acetonitrile / 0.1% (v/v) TFA at a flow rate of 1 ml per minute.

D. pCHO1/NR6/FLAG

In order to determine the native N termini of NR6, a C terminal FLAG NR6 CHO cell line was established.

The plasmid pKUSA166 (murine NR6 cDNA cloned into the EcoR I site of pBLUESCRIPT) was digested with BamH I to remove the sequences encoding the last 15 amino acids of murine NR6. Synthetic oligonucleotides which encode the

3' end of mouse NR6 followed by the FLAG peptide tag were annealed and ligated into the BamH I site of pKUSA166. The sequence of the oligonucleotides was as follows:-

5

I L P S G R R G A A R G P A G D Y K D
D D D K * [SEQ ID NO:34]
GATCTTGCCCTCGGGCAGACGGGGTGCGGCGAGAGGTCCTGCCGCGACTACAAGG
10 ACGACGATGACAAGTA G [SEQ ID NO:33]
AACGGGAGCCCGTCTGCCCCACGCCGCTCTCCAGGACGGCCGCTGATGTTCTGCT
GCTACTGTTTCATCCTAG [SEQ ID NO:35]

The 5' end of the linker introduces a silent mutation
15 (CTG > TTG), to destroy the 5' BamH I site upon
insertion of the linker. The NR6 cDNA (with native
signal sequence) with the C-terminal FLAG was cut out of
pKUSA166 with EcoR I and BamH I and cloned into the EcoR
I - BamH I cloning sites of pCHO-1. This vector results
20 in the secretion of NR6 protein with a C-terminal flag
tag (CN FLAG-mRN6).

This vector results in the secretion of NR6 protein from
KUSA cells. The vector pCHO1 has been previously
25 described in (17) although with a different secretable
marker.

(i) Production of polyclonal NR6 antiserum

30 The following peptide from the N terminal area of NR6
was chosen for production of polyclonal antiserum to NR6

VISPQDPTLLIGSSLQATCSIHGDTP [SEQ ID NO:39]

35 The peptide was conjugated to KLH and injected into
rabbits. Production and purification of the polyclonal
antibody specific to the NR6 peptide sequence follows

standard methods.

(ii) Protein expression

5 KUSA cells transfected with cDNA of C terminal tagged mNR6 were grown to confluence in flasks (800ml) using IMDM media containing 10% (v/v) FBS. Conditioned media (100 ml) was harvested 3 -4 days post confluence.

10 (iii) Characterisation of NR6 by Immunoprecipitation and Western blotting

In order to establish that NR6 with the predicted sequence is produced in KUSA cells transfected with the
15 cDNA, western blot analysis using both M2 antibody and purified NR6 specific rabbit antibody were performed. Conditioned media (1 to 5 ml) was immunoprecipitated with M2 affinity resin (10-20 Fl). Then after sufficient time for binding, the beads were washed with MT-PBS and
20 subsequently NR6 eluted with 100 Fg/ml FLAG peptide (40 Fl, (1, 5 minute incubation). The sample was then subjected to reducing and non reducing SDS PAGE followed by western blot analysis. Both purified NR6 polyclonal antibody (purified by protein G) and M2 antibody
25 recognise a band under reducing conditions of a molecular weight size approximately 65,000 daltons. Since the two antibodies recognising resides at the N terminus and C terminus it is reasonable to assume that full length NR6 is produced. Biotinylation of the
30 respective antibodies by standard methods reduces the background. Under non-reducing conditions polyclonal NR6 bind antibodies to a band of a molecular weight of approximately 127,000, consistent with a dimeric NR6 disulphide linked form. Minor components of tetrameric
35 NR6 are present, no monomeric NR6 is evident using polyclonal NR6 antibodies.

EXAMPLE 15

Generation of NR6 knockout mice

To construct the NR6 targeting vector, 4.1kb of genomic NR6 DNA containing exons 2 through to 6 was deleted and replaced with G418-resistance cassette, leaving 5N and 3N NR6 arms of 2.9 and 4.5 kb respectively. A 4.5 kb XhoI fragment of the murine genomic NR6 clone 2.2 (Figure 3) containing exons 7, 8 and 3N flanking sequence was subcloned into the XhoI site of pBluescript generating pBSNR6Xho4.5. A 2.9kb NotI-StuI fragment within NR6 intron 1 from the same genomic clone was inserted into NotI and EcoRV digested pBSNR6Xho4.5 creating pNR6-Ex2-6. This plasmid was digested with ClaI, which was situated between the two NR6 fragments, and following blunt ending, ligated with a blunted 6kb HindIII fragment from placZneo, which contains the lacZgene and a PGKneo cassette, to generate the final targeting vector, pNR6lacZneo. pNR6lacZneo was linearised with NotI and electroporated into W9.5 embryonic stem cells. After 48 hours, transfected cells were selected in 175 Fg/ml G418 and resistant clones picked and expanded after a further 8 days.

Clones in which the targetting vector had recombined with the endogenous NR6 gene were identified by hybridising SpeI-digested genomic DNA with a 0.6 kb XhoI-StuI fragment from genomic NR6 clone 2.2. This probe (probe A, Figure 4), which is located 3N to the NR6 sequences in the targeting vector, distinguished between the endogenous (9.9 kb) and targeted (7.1 kb) NR6 loci (Figure 5).

Genomic DNA was digested with SpeI for 16hrs at 37°C, electrophoresed through 0.8% (w/v) agarose, transferred to nylon membranes and hybridised to ³²P-labelled probe in a solution containing 0.5M sodium phosphate, 7% (w/v)

SDS, 1mM EDTA and washed in a solution containing 40mM sodium phosphate, 1% (w/v) SDS at 65°C. Hybridising bands were visualised by autoradiography for 16 hours at -70°C using Kodak XAR-5 film and intensifying screens.

5 Two targeted ES cell clones, W9.5NR6-2-44 and W9.5NR6-4-2, were injected into C57Bl/6 blastocysts to generate chimeric mice. Male chimeras were mated with C57Bl/6 females to yield NR6 heterozygotes which were subsequently interbred to produce wild-type (NR6^{+/+}),

10 heterozygous (NR6^{+/-}) and mutant (NR6^{-/-}) mice. The genotypes of offspring were determined by Southern Blot analysis of genomic DNA extracted from tail biopsies.

Genotyping of mice at weaning from matings between NR6^{+/-} heterozygous mice derived from both targeted ES cell clones revealed an absence of homozygous NR6^{-/-} mutants. As no unusual loss of mice was observed between birth and weaning, this suggests that lack of NR6 is lethal during embryonic development or immediately after birth.

20 Genotyping of embryonic tissues at various stages of development suggests that death occurs late in gestation (beyond day 16) or at birth.

EXAMPLE 16

25 Oligonucleotides

1943:

5' GTC CAA GTG CGT TGT AAC CCA 3'

2070:

5' GCT GAG TGT GCG CTG GGT CTC ACC 3'

30 2057:

5' GGC TCC ACT CGC TCC AGA 3'

Those skilled in the art will appreciate that the invention described herein is susceptible to variations

35 and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The

invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said
5 steps or features.

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(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
30 (C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version
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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 5 amino acids

(B) TYPE: amino acid

20

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

25

Trp Ser Xaa Trp Ser

30

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: base pairs

(B) TYPE: nucleic acid

35

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

5

ACTCGCTCCA GATTCCCGCC TTTT

24

10 (2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs

(B) TYPE: nucleic acid

15 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

25 TCCCGCCTTT TTCGACCCAT AGAT

24

(2) INFORMATION FOR SEQ ID NO:4:

30 (i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

35

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

GGTACTTGGC TTGGAAGAGG AAAT

24

(2) INFORMATION FOR SEQ ID NO:5:

5

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 24 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

10 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

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24

(2) INFORMATION FOR SEQ ID NO:6:

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(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

25 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

AGCTGCTGTT AAAGGGCTTC TC

22

35

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Oligonucleotide

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

(A/G) CTCCA (A/G) TC (A/G) CTCCA

15

15

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

- 20 (A) LENGTH: 15 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

25

(ii) MOLECULE TYPE: Oligonucleotide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

30 (A/G) CTCCA (C/T) TC (A/G) CTCCA

15

(2) INFORMATION FOR SEQ ID NO:9:

35

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 21 base pairs

- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

5 (ii) MOLECULE TYPE: DNA

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

AAGTGTGACC ATCATGTGGA C

21

15 (2) INFORMATION FOR SEQ ID NO:10:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 18 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

20

(ii) MOLECULE TYPE: DNA

25

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

30 GGAGGTGTTA AGGAGGCG

18

(2) INFORMATION FOR SEQ ID NO:11:

- 35 (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 18 base pairs
 - (B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

10

ATGCCCCGCGG GTCGCCCCG

18

15 (2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1506 base pairs

(B) TYPE: nucleic acid

20 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

25

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..1242

30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

GGCACGAGCT TCGCTGTCCG CGCCAGTGA CGCGCGTGCG GACCCGAGCC CCAATCTGCA -64
35 CCCCCGAGAC TCGCCCCCGC CCCATACCGG CGTTGCAGTC ACCGCCCCGTT GCGCGCCACC -4
CCC -3
ATG CCC GCG GGT CGC CCG GGC CCC GTC GCC CAA TCC GCG CGG CGG CCG 48

	Met	Pro	Ala	Gly	Arg	Pro	Gly	Pro	Val	Ala	Gln	Ser	Ala	Arg	Arg	Pro	
	1					5					10				15		
	CCG	CGG	CCG	CTG	TCC	TCG	CTG	TGG	TCG	CCT	CTG	TTG	CTC	TGT	GTC	CTC	96
5	Pro	Arg	Pro	Leu	Ser	Ser	Leu	Trp	Ser	Pro	Leu	Leu	Leu	Cys	Val	Leu	
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10			35					40					45				
	CAG	GAC	CCC	ACC	CTT	CTC	ATC	GGC	TCC	TCC	CTG	CAA	GCT	ACC	TGC	TCT	192
	Gln	Asp	Pro	Thr	Leu	Leu	Ile	Gly	Ser	Ser	Leu	Gln	Ala	Thr	Cys	Ser	
		50					55					60					
15	ATA	CAT	GGA	GAC	ACA	CCT	GGG	GCC	ACC	GCT	GAG	GGG	CTC	TAC	TGG	ACC	240
	Ile	His	Gly	Asp	Thr	Pro	Gly	Ala	Thr	Ala	Glu	Gly	Leu	Tyr	Trp	Thr	
		65				70					75				80		
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20	Leu	Asn	Gly	Arg	Arg	Leu	Pro	Ser	Glu	Leu	Ser	Arg	Leu	Leu	Asn	Thr	
				85					90				95				
	TCC	ACC	CTG	GCC	CTG	GCC	CTG	GCT	AAC	CTT	AAT	GGG	TCC	AGG	CAG	CAG	336
25	Ser	Thr	Leu	Ala	Leu	Ala	Leu	Ala	Asn	Leu	Asn	Gly	Ser	Arg	Gln	Gln	
				100				105					110				
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30			115					120					125				
	GGC	TCC	TGC	CTC	TAT	GTT	GGC	TTG	CCC	CCT	GAG	AAG	CCC	TTT	AAC	ATC	432
	Gly	Ser	Cys	Leu	Tyr	Val	Gly	Leu	Pro	Pro	Glu	Lys	Pro	Phe	Asn	Ile	
			130				135					140					
35																	

- 79 -

	GTG GTG GAT GAC GTC AGC AAC CAG ACC TCC TGC CGT CTC GCG GGC CTG	912
	Val Val Asp Asp Val Ser Asn Gln Thr Ser Cys Arg Leu Ala Gly Leu	
	290 295 300	
5	AAG CCC GGC ACC GTT TAC TTC GTC CAA GTG CGT TGT AAC CCA TTC GGG	960
	Lys Pro Gly Thr Val Tyr Phe Val Gln Val Arg Cys Asn Pro Phe Gly	
	305 310 315 320	
10	ATC TAT GGG TCG AAA AAG GCG GGA ATC TGG AGC GAG TGG AGC CAC CCC	1008
	Ile Tyr Gly Ser Lys Lys Ala Gly Ile Trp Ser Glu Trp Ser His Pro	
	325 330 335	
15	ACC GCT GCC TCC ACC CCT CGA AGT GAG CGC CCG GGC CCG GGC GGC GGG	1056
	Thr Ala Ala Ser Thr Pro Arg Ser Glu Arg Pro Gly Pro Gly Gly Gly	
	340 345 350	
20	GTG TGC GAG CCG CGG GGC GGC GAG CCC AGC TCG GGC CCG GTG CGG CGC	1104
	Val Cys Glu Pro Arg Gly Gly Glu Pro Ser Ser Gly Pro Val Arg Arg	
	355 360 365	
25	GAG CTC AAG CAG TTC CTC GGC TGG CTC AAG AAG CAC GCA TAC TGC TCG	1152
	Glu Leu Lys Gln Phe Leu Gly Trp Leu Lys Lys His Ala Tyr Cys Ser	
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30	AAC CTT AGT TTC CGC CTG TAC GAC CAG TGG CGT GCT TGG ATG CAG AAG	1200
	Asn Leu Ser Phe Arg Leu Tyr Asp Gln Trp Arg Ala Trp Met Gln Lys	
	385 390 395 400	
35	TCA CAC AAG ACC CGA AAC CAG GTC CTG CCG GCT AAA CTC TAAGGATAGG	1249
	Ser His Lys Thr Arg Asn Gln Val Leu Pro Ala Lys Leu	
	405 410	
	CCATCCTCCT GCTGGGTCAG ACCTGGAGGC TCACCTGAAT TGGAGCCCCCT CTGTACCATC	1309
	TGGGCAACAA AGAAACCTAC CAGAGGCTGG GGCACAATGA GCTCCCACAA CCACAGCTTT	1369
	GGTCCACATG ATGGTCACAC TTGGATATAC CCCAGTGTGG GTAAGGTTGG GGTATTGCAG	1429

GGCCTCCCAA CAATCTCTTT AAATAAATAA AGGAGTTGTT CAGGTAAAAA AAAAAAAAAA 1489

AAAAAAAAAA AAAAAAA 1506

5

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 413 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Met Pro Ala Gly Arg Pro Gly Pro Val Ala Gln Ser Ala Arg Arg Pro
 1 5 10 15

Pro Arg Pro Leu Ser Ser Leu Trp Ser Pro Leu Leu Leu Cys Val Leu
 20 25 30

Gly Val Pro Arg Gly Gly Ser Gly Ala His Thr Ala Val Ile Ser Pro
 35 40 45

Gln Asp Pro Thr Leu Leu Ile Gly Ser Ser Leu Gln Ala Thr Cys Ser
 50 55 60

Ile His Gly Asp Thr Pro Gly Ala Thr Ala Glu Gly Leu Tyr Trp Thr
 30 65 70 75 80

Leu Asn Gly Arg Arg Leu Pro Ser Glu Leu Ser Arg Leu Leu Asn Thr
 85 90 95

Ser Thr Leu Ala Leu Ala Leu Ala Asn Leu Asn Gly Ser Arg Gln Gln
 100 105 110

	Ser Gly Asp Asn Leu Val Cys His Ala Arg Asp Gly Ser Ile Leu Ala	
	115	120 125
5	Gly Ser Cys Leu Tyr Val Gly Leu Pro Pro Glu Lys Pro Phe Asn Ile	
	130	135 140
	Ser Cys Trp Ser Arg Asn Met Lys Asp Leu Thr Cys Arg Trp Thr Pro	
	145	150 155 160
10	Gly Ala His Gly Glu Thr Phe Leu His Thr Asn Tyr Ser Leu Lys Tyr	
	165	170 175
	Lys Leu Arg Trp Tyr Gly Gln Asp Asn Thr Cys Glu Glu Tyr His Thr	
	180	185 190
15	Val Gly Pro His Ser Cys His Ile Pro Lys Asp Leu Ala Leu Phe Thr	
	195	200 205
	Pro Tyr Glu Ile Trp Val Glu Ala Thr Asn Arg Leu Gly Ser Ala Arg	
20	210	215 220
	Ser Asp Val Leu Thr Leu Asp Val Leu Asp Val Val Thr Thr Asp Pro	
	225	230 235 240
25	Pro Pro Asp Val His Val Ser Arg Val Gly Gly Leu Glu Asp Gln Leu	
	245	250 255
	Ser Val Arg Trp Val Ser Pro Pro Ala Leu Lys Asp Phe Leu Phe Gln	
	260	265 270
30	Ala Lys Tyr Gln Ile Arg Tyr Arg Val Glu Asp Ser Val Asp Trp Lys	
	275	280 285
	Val Val Asp Asp Val Ser Asn Gln Thr Ser Cys Arg Leu Ala Gly Leu	
35	290	295 300

Lys Pro Gly Thr Val Tyr Phe Val Gln Val Arg Cys Asn Pro Phe Gly
 305 310 315 320
 Ile Tyr Gly Ser Lys Lys Ala Gly Ile Trp Ser Glu Trp Ser His Pro
 5 325 330 335
 Thr Ala Ala Ser Thr Pro Arg Ser Glu Arg Pro Gly Pro Gly Gly Gly
 340 345 350
 Val Cys Glu Pro Arg Gly Gly Glu Pro Ser Ser Gly Pro Val Arg Arg
 10 355 360 365
 Glu Leu Lys Gln Phe Leu Gly Trp Leu Lys Lys His Ala Tyr Cys Ser
 370 375 380
 Asn Leu Ser Phe Arg Leu Tyr Asp Gln Trp Arg Ala Trp Met Gln Lys
 15 385 390 395 400
 Ser His Lys Thr Arg Asn Gln Val Leu Pro Ala Lys Leu
 20 405 410

(2) INFORMATION FOR SEQ ID NO:14:

25

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1549 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 30 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

35

(ix) FEATURE:

- (A) NAME/KEY: CDS
 (B) LOCATION: 1..1278

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

5 GGCACGAGCT TCGCTGTCCG CGCCCAGTGA CGCGCGTGCG GACCCGAGCC CCAATCTGCA -65
 CCCC GCAGAC TCGCCCCCGC CCCATACCGG CGTTGCAGTC ACCGCCCGTT GCGCGCCACC -5
 CCCA -1
 10 ATG CCC GCG GGT CGC CCG GGC CCC GTC GCC CAA TCC GCG CGG CGG CCG 48
 Met Pro Ala Gly Arg Pro Gly Pro Val Ala Gln Ser Ala Arg Arg Pro
 1 5 10 15
 15 CCG CGG CCG CTG TCC TCG CTG TGG TCG CCT CTG TTG CTC TGT GTC CTC 96
 Pro Arg Pro Leu Ser Ser Leu Trp Ser Pro Leu Leu Leu Cys Val Leu
 20 25 30
 20 GGG GTG CCT CGG GGC GGA TCG GGA GCC CAC ACA GCT GTA ATC AGC CCC 144
 Gly Val Pro Arg Gly Gly Ser Gly Ala His Thr Ala Val Ile Ser Pro
 35 40 45
 25 CAG GAC CCC ACC CTT CTC ATC GGC TCC TCC CTG CAA GCT ACC TGC TCT 192
 Gln Asp Pro Thr Leu Leu Ile Gly Ser Ser Leu Gln Ala Thr Cys Ser
 50 55 60
 30 ATA CAT GGA GAC ACA CCT GGG GCC ACC GCT GAG GGG CTC TAC TGG ACC 240
 Ile His Gly Asp Thr Pro Gly Ala Thr Ala Glu Gly Leu Tyr Trp Thr
 65 70 75 80
 35 CTC AAT GGT CGC CGC CTG CCC TCT GAG CTG TCC CGC CTC CTT AAC ACC 288
 Leu Asn Gly Arg Arg Leu Pro Ser Glu Leu Ser Arg Leu Leu Asn Thr
 85 90 95
 40 TCC ACC CTG GCC CTG GCC CTG GCT AAC CTT AAT GGG TCC AGG CAG CAG 336
 Ser Thr Leu Ala Leu Ala Leu Ala Asn Leu Asn Gly Ser Arg Gln Gln
 100 105 110

	TCA GGA GAC AAT CTG GTG TGT CAC GCC CGA GAC GGC AGC ATT CTG GCT	384
	Ser Gly Asp Asn Leu Val Cys His Ala Arg Asp Gly Ser Ile Leu Ala	
	115 120 125	
5	GGC TCC TGC CTC TAT GTT GGC TTG CCC CCT GAG AAG CCC TTT AAC ATC	432
	Gly Ser Cys Leu Tyr Val Gly Leu Pro Pro Glu Lys Pro Phe Asn Ile	
	130 135 140	
10	AGC TGC TGG TCC CGG AAC ATG AAG GAT CTC ACG TGC CGC TGG ACA CCG	480
	Ser Cys Trp Ser Arg Asn Met Lys Asp Leu Thr Cys Arg Trp Thr Pro	
	145 150 155 160	
15	GGT GCA CAC GGG GAG ACA TTC TTA CAT ACC AAC TAC TCC CTC AAG TAC	528
	Gly Ala His Gly Glu Thr Phe Leu His Thr Asn Tyr Ser Leu Lys Tyr	
	165 170 175	
20	AAG CTG AGG TGG TAC GGT CAG GAT AAC ACA TGT GAG GAG TAC CAC ACT	576
	Lys Leu Arg Trp Tyr Gly Gln Asp Asn Thr Cys Glu Glu Tyr His Thr	
	180 185 190	
25	GTG GGC CCT CAC TCA TGC CAT ATC CCC AAG GAC CTG GCC CTC TTC ACT	624
	Val Gly Pro His Ser Cys His Ile Pro Lys Asp Leu Ala Leu Phe Thr	
	195 200 205	
30	CCC TAT GAG ATC TGG GTG GAA GCC ACC AAT CGC CTA GGC TCA GCA AGA	672
	Pro Tyr Glu Ile Trp Val Glu Ala Thr Asn Arg Leu Gly Ser Ala Arg	
	210 215 220	
35	TCT GAT GTC CTC ACA CTG GAT GTC CTG GAC GTG GTG ACC ACG GAC CCC	720
	Ser Asp Val Leu Thr Leu Asp Val Leu Asp Val Val Thr Thr Asp Pro	
	225 230 235 240	
40	CCA CCC GAC GTG CAC GTG AGC CGC GTT GGG GGC CTG GAG GAC CAG CTG	768
	Pro Pro Asp Val His Val Ser Arg Val Gly Gly Leu Glu Asp Gln Leu	
	245 250 255	

	AGT GTG CGC TGG GTC TCA CCA CCA GCT CTC AAG GAT TTC CTC TTC CAA	816
	Ser Val Arg Trp Val Ser Pro Pro Ala Leu Lys Asp Phe Leu Phe Gln	
	260 265 270	
5	GCC AAG TAC CAG ATC CGC TAC CGC GTG GAG GAC AGC GTG GAC TGG AAG	864
	Ala Lys Tyr Gln Ile Arg Tyr Arg Val Glu Asp Ser Val Asp Trp Lys	
	275 280 285	
10	GTG GTG GAT GAC GTC AGC AAC CAG ACC TCC TGC CGT CTC GCG GGC CTG	912
	Val Val Asp Asp Val Ser Asn Gln Thr Ser Cys Arg Leu Ala Gly Leu	
	290 295 300	
15	AAG CCC GGC ACC GTT TAC TTC GTC CAA GTG CGT TGT AAC CCA TTC GGG	960
	Lys Pro Gly Thr Val Tyr Phe Val Gln Val Arg Cys Asn Pro Phe Gly	
	305 310 315 320	
20	ATC TAT GGG TCG AAA AAG GCG GGA ATC TGG AGC GAG TGG AGC CAC CCC	1008
	Ile Tyr Gly Ser Lys Lys Ala Gly Ile Trp Ser Glu Trp Ser His Pro	
	325 330 335	
25	ACC GCT GCC TCC ACC CCT CGA AGT GAG CGC CCG GGC CCG GGC GGC GGG	1056
	Thr Ala Ala Ser Thr Pro Arg Ser Glu Arg Pro Gly Pro Gly Gly Gly	
	340 345 350	
30	GTG TGC GAG CCG CGG GGC GGC GAG CCC AGC TCG GGC CCG GTG CGG CGC	1104
	Val Cys Glu Pro Arg Gly Gly Glu Pro Ser Ser Gly Pro Val Arg Arg	
	355 360 365	
35	GAG CTC AAG CAG TTC CTC GGC TGG CTC AAG AAG CAC GCA TAC TGC TCG	1152
	Glu Leu Lys Gln Phe Leu Gly Trp Leu Lys Lys His Ala Tyr Cys Ser	
	370 375 380	
40	AAC CTT AGT TTC CGC CTG TAC GAC CAG TGG CGT GCT TGG ATG CAG AAG	1200
	Asn Leu Ser Phe Arg Leu Tyr Asp Gln Trp Arg Ala Trp Met Gln Lys	
	385 390 395 400	

TCA CAC AAG ACC CGA AAC CAG GAC GAG GGG ATC CTG CCT TCG GGC AGA 1248
 Ser His Lys Thr Arg Asn Gln Asp Glu Gly Ile Leu Pro Ser Gly Arg
 405 410 415

5 CGG GGT GCG GCG AGA GGT CCT GCC GGT TAAACTCTAA GGATAGGCCA 1295
 Arg Gly Ala Ala Arg Gly Pro Ala Gly
 420 425

10 TCCTCCTGCT GGGTCAGACC TGGAGGCTCA CCTGAATTGG AGCCCCTCTG TACCATCTGG 1355
 GCAACAAAGA AACCTACCAG AGGCTGGGGC ACAATGAGCT CCCACAACCA CAGCTTTGGT 1415
 CCACATGATG GTCACACTTG GATATACCCC AGTGTGGGTA AGGTTGGGGT ATTGCAGGGC 1475

15 CTCCCAACAA TCTCTTTAAA TAAATAAAGG AGTTGTTCAG GTAAAAAAAA AAAAAAAAAA 1535
 AAAAAAAAAA AAAA 1549

20

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 425 amino acids
 25 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Met Pro Ala Gly Arg Pro Gly Pro Val Ala Gln Ser Ala Arg Arg Pro
 1 5 10 15

35 Pro Arg Pro Leu Ser Ser Leu Trp Ser Pro Leu Leu Leu Cys Val Leu
 20 25 30

	Gly Val Pro Arg Gly Gly Ser Gly Ala His Thr Ala Val Ile Ser Pro	
	35	40 45
	Gln Asp Pro Thr Leu Leu Ile Gly Ser Ser Leu Gln Ala Thr Cys Ser	
5	50	55 60
	Ile His Gly Asp Thr Pro Gly Ala Thr Ala Glu Gly Leu Tyr Trp Thr	
	65	70 75 80
10	Leu Asn Gly Arg Arg Leu Pro Ser Glu Leu Ser Arg Leu Leu Asn Thr	
	85	90 95
	Ser Thr Leu Ala Leu Ala Leu Ala Asn Leu Asn Gly Ser Arg Gln Gln	
	100	105 110
15	Ser Gly Asp Asn Leu Val Cys His Ala Arg Asp Gly Ser Ile Leu Ala	
	115	120 125
	Gly Ser Cys Leu Tyr Val Gly Leu Pro Pro Glu Lys Pro Phe Asn Ile	
20	130	135 140
	Ser Cys Trp Ser Arg Asn Met Lys Asp Leu Thr Cys Arg Trp Thr Pro	
	145	150 155 160
25	Gly Ala His Gly Glu Thr Phe Leu His Thr Asn Tyr Ser Leu Lys Tyr	
	165	170 175
	Lys Leu Arg Trp Tyr Gly Gln Asp Asn Thr Cys Glu Glu Tyr His Thr	
	180	185 190
30	Val Gly Pro His Ser Cys His Ile Pro Lys Asp Leu Ala Leu Phe Thr	
	195	200 205
	Pro Tyr Glu Ile Trp Val Glu Ala Thr Asn Arg Leu Gly Ser Ala Arg	
35	210	215 220

	Ser Asp Val Leu Thr Leu Asp Val Leu Asp Val Val Thr Thr Asp Pro	
	225	230 235 240
5	Pro Pro Asp Val His Val Ser Arg Val Gly Gly Leu Glu Asp Gln Leu	
	245	250 255
	Ser Val Arg Trp Val Ser Pro Pro Ala Leu Lys Asp Phe Leu Phe Gln	
	260	265 270
10	Ala Lys Tyr Gln Ile Arg Tyr Arg Val Glu Asp Ser Val Asp Trp Lys	
	275	280 285
	Val Val Asp Asp Val Ser Asn Gln Thr Ser Cys Arg Leu Ala Gly Leu	
	290	295 300
15	Lys Pro Gly Thr Val Tyr Phe Val Gln Val Arg Cys Asn Pro Phe Gly	
	305	310 315 320
	Ile Tyr Gly Ser Lys Lys Ala Gly Ile Trp Ser Glu Trp Ser His Pro	
20	325	330 335
	Thr Ala Ala Ser Thr Pro Arg Ser Glu Arg Pro Gly Pro Gly Gly Gly	
	340	345 350
25	Val Cys Glu Pro Arg Gly Gly Glu Pro Ser Ser Gly Pro Val Arg Arg	
	355	360 365
	Glu Leu Lys Gln Phe Leu Gly Trp Leu Lys Lys His Ala Tyr Cys Ser	
	370	375 380
30	Asn Leu Ser Phe Arg Leu Tyr Asp Gln Trp Arg Ala Trp Met Gln Lys	
	385	390 395 400
	Ser His Lys Thr Arg Asn Gln Asp Glu Gly Ile Leu Pro Ser Gly Arg	
35	405	410 415

Arg Gly Ala Ala Arg Gly Pro Ala Gly

PCT/GB97/02479

420

425

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(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 938 base pairs

10

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

15

(ix) FEATURE:

(A) NAME/KEY: CDS

(B) LOCATION: 1..468

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

25 GGC ACC GTT TAC TTC GTC CAA GTG CGT TGT AAC CCA TTC GGG ATC TAT 48

Gly Thr Val Tyr Phe Val Gln Val Arg Cys Asn Pro Phe Gly Ile Tyr

1 5 10 15

GGG TCG AAA AAG GCG GGA ATC TGG AGC GAG TGG AGC CAC CCC ACC GCT 96

30 Gly Ser Lys Lys Ala Gly Ile Trp Ser Glu Trp Ser His Pro Thr Ala

20 25 30

GCC TCC ACC CCT CGA AGT GAG CGC CCG GGC CCG GGC GGC GGG GTG TGC 144

Ala Ser Thr Pro Arg Ser Glu Arg Pro Gly Pro Gly Gly Gly Val Cys

35

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	GAG CCG CGG GGC GGC GAG CCC AGC TCG GGC CCG GTG CGG CGC GAG CTC	192
	Glu Pro Arg Gly Gly Glu Pro Ser Ser Gly Pro Val Arg Arg Glu Leu	
	50 55 60	
5	AAG CAG TTC CTC GGC TGG CTC AAG AAG CAC GCA TAC TGC TCG AAC CTT	240
	Lys Gln Phe Leu Gly Trp Leu Lys Lys His Ala Tyr Cys Ser Asn Leu	
	65 70 75 80	
10	AGT TTC CGC CTG TAC GAC CAG TGG CGT GCT TGG ATG CAG AAG TCA CAC	288
	Ser Phe Arg Leu Tyr Asp Gln Trp Arg Ala Trp Met Gln Lys Ser His	
	85 90 95	
15	AAG ACC CGA AAC CAG GTA GGA AAG TTG GGG GAG GCT TGC GTG GGG GGT	336
	Lys Thr Arg Asn Gln Val Gly Lys Leu Gly Glu Ala Cys Val Gly Gly	
	100 105 110	
20	AAA GGA GCA GAG GAA GAG AGA GAC CCG GGT GAG CAG CCT CCA CAA CAC	384
	Lys Gly Ala Glu Glu Glu Arg Asp Pro Gly Glu Gln Pro Pro Gln His	
	115 120 125	
	CGC ACT CTT CTT TCC AAG CAC AGG ACG AGG GGA TCC TGC CCT CGG GCA	432
	Arg Thr Leu Leu Ser Lys His Arg Thr Arg Gly Ser Cys Pro Arg Ala	
	130 135 140	
25	GAC GGG GTG CGG CGA GAG GTA AGG GGG TCT GGG TGAGTGGGGC CTACAGCAGT	485
	Asp Gly Val Arg Arg Glu Val Arg Gly Ser Gly	
	145 150 155	
30	CTAGATGAGG CCCTTTCCCC TCCTTCGGTG TTGCTCAAAG GGATCTCTTA GTGCTCATTT	545
	CACCCACTGC AAAGAGCCCC AGGTTTTACT GCATCATCAA GTTGCTGAAG GGTCCAGGCT	605
	TAATGTGGCC TCTTTTCTGC CCTCAGGTCC TGCCGGCTAA ACTCTAAGGA TAGGCCATCC	665
35	TCCTGCTGGG TCAGACCTGG AGGCTCACCT GAATTGGAGC CCCTCTGTAC CTATCTGGGC	725
	AACAAAGAAA CCTACCATGA GGCTGGGGCA CAATGAGCTC CCACAACCAC AGCTTTGGTC	785

CACATGATGG TCACACTTGG ATATACCCCA GTGTGGGTAA GGTGGGGTA TTGCAGGGCC 845
 TCCCAACAAT CTCTTTAAAT AAATAAGGA GTTGTTTCAGG TAAAAAAAAA AAAAAAAAAA 905
 5 AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAA 938

(2) INFORMATION FOR SEQ ID NO:17:

10 (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 155 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

15 (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Gly Thr Val Tyr Phe Val Gln Val Arg Cys Asn Pro Phe Gly Ile Tyr
 20 1 5 10 15
 Gly Ser Lys Lys Ala Gly Ile Trp Ser Glu Trp Ser His Pro Thr Ala
 20 25 30
 25 Ala Ser Thr Pro Arg Ser Glu Arg Pro Gly Pro Gly Gly Val Cys
 35 40 45
 Glu Pro Arg Gly Gly Glu Pro Ser Ser Gly Pro Val Arg Arg Glu Leu
 50 55 60
 30 Lys Gln Phe Leu Gly Trp Leu Lys Lys His Ala Tyr Cys Ser Asn Leu
 65 70 75 80
 Ser Phe Arg Leu Tyr Asp Gln Trp Arg Ala Trp Met Gln Lys Ser His
 35 85 90 95

Lys Thr Arg Asn Gln Val Gly Lys Leu Gly Glu Ala Cys Val Gly Gly
 100 105 110
 Lys Gly Ala Glu Glu Glu Arg Asp Pro Gly Glu Gln Pro Pro Gln His
 5 115 120 125
 Arg Thr Leu Leu Ser Lys His Arg Thr Arg Gly Ser Cys Pro Arg Ala
 130 135 140
 10 Asp Gly Val Arg Arg Glu Val Arg Gly Ser Gly
 145 150 155

15 (2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 834 base pairs
 (B) TYPE: nucleic acid
 20 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

25

(ix) FEATURE:

- (A) NAME/KEY: CDS
 (B) LOCATION: 1..834

30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

CCC ACC CTT CTC ATC GGC TCC TCC CTG CAA GCT ACC TGC TCT ATA CAT 98
 Pro Thr Leu Leu Ile Gly Ser Ser Leu Gln Ala Thr Cys Ser Ile His
 35 51 55 60 65

	GGA GAC ACA CCT GGG GCC ACC GCT GAG GGG CTC TAC TGG ACC CTC AAT	146
	Gly Asp Thr Pro Gly Ala Thr Ala Glu Gly Leu Tyr Trp Thr Leu Asn	
	70 75 80	
5	GGT CGC CGC CTG CCC TCT GAG CTG TCC CGC CTC CTT AAC ACC TCC ACC	194
	Gly Arg Arg Leu Pro Ser Glu Leu Ser Arg Leu Leu Asn Thr Ser Thr	
	85 90 95	
10	CTG GCC CTG GCC CTG GCT AAC CTT AAT GGG TCC AGG CAG CAG TCA GGA	242
	Leu Ala Leu Ala Leu Ala Asn Leu Asn Gly Ser Arg Gln Gln Ser Gly	
	100 105 110	
15	GAC AAT CTG GTG TGT CAC GCC CGA GAC GGC AGC ATT CTG GCT GGC TCC	290
	Asp Asn Leu Val Cys His Ala Arg Asp Gly Ser Ile Leu Ala Gly Ser	
	115 120 125 130	
20	TGC CTC TAT GTT GGC TTG CCC CCT GAG AAG CCC TTT AAC ATC AGC TGC	338
	Cys Leu Tyr Val Gly Leu Pro Pro Glu Lys Pro Phe Asn Ile Ser Cys	
	135 140 145	
25	TGG TCC CGG AAC ATG AAG GAT CTC ACG TGC CGC TGG ACA CCG GGT GCA	386
	Trp Ser Arg Asn Met Lys Asp Leu Thr Cys Arg Trp Thr Pro Gly Ala	
	150 155 200	
30	CAC GGG GAG ACA TTC TTA CAT ACC AAC TAC TCC CTC AAG TAC AAG CTG	434
	His Gly Glu Thr Phe Leu His Thr Asn Tyr Ser Leu Lys Tyr Lys Leu	
	205 210 215	
35	AGG TGG TAC GGT CAG GAT AAC ACA TGT GAG GAG TAC CAC ACT GTG GGG	482
	Arg Trp Tyr Gly Gln Asp Asn Thr Cys Glu Glu Tyr His Thr Val Gly	
	220 225 230	
40	CCC CAC TCA TGC CAT ATC CCC AAG GAC CTG GCC CTC TTC ACT CCC TAT	530
	Pro His Ser Cys His Ile Pro Lys Asp Leu Ala Leu Phe Thr Pro Tyr	
	235 240 245 250	

	GAG ATC TGG GTG GAA GCC ACC AAT CGC CTA GGC TCA GCA AGA TCT GAT	578
	Glu Ile Trp Val Glu Ala Thr Asn Arg Leu Gly Ser Ala Arg Ser Asp	
	255 260 265	
5	GTC CTC ACA CTG GAT GTC CTG GAC GTG GTG ACC ACG GAC CCC CCA CCC	626
	Val Leu Thr Leu Asp Val Leu Asp Val Val Thr Thr Asp Pro Pro Pro	
	270 275 280	
10	GAC GTG CAC GTG AGC CGC GTT GGG GGC CTG GAG GAC CAG CTG AGT GTG	674
	Asp Val His Val Ser Arg Val Gly Gly Leu Glu Asp Gln Leu Ser Val	
	285 290 295	
15	CGC TGG GTC TCA CCA CCA GCT CTC AAG GAT TTC CTC TTC CAA GCC AAG	722
	Arg Trp Val Ser Pro Pro Ala Leu Lys Asp Phe Leu Phe Gln Ala Lys	
	300 305 310	
20	TAC CAG ATC CGC TAC CGC GTG GAG GAC AGC GTG GAC TGG AAG GTG GTG	770
	Tyr Gln Ile Arg Tyr Arg Val Glu Asp Ser Val Asp Trp Lys Val Val	
	315 320 325 330	
	GAT GAC GTC AGC AAC CAG ACC TCC TGC CGT CTC GCG GGC CTG AAG CCC	818
	Asp Asp Val Ser Asn Gln Thr Ser Cys Arg Leu Ala Gly Leu Lys Pro	
	335 340 345	
25	GGC ACC GTT TAC TTC GTC CAA GTG CGT TGT AAC CCA TTC GGG ATC TAT	866
	Gly Thr Val Tyr Phe Val Gln Val Arg Cys Asn Pro Phe Gly Ile Tyr	
	350 355 360	
30	GGG TCG AAA AAG GCG GGA	894
	Gly Ser Lys Lys Ala Gly	
	365	

(2) INFORMATION FOR SEQ ID NO:19:

35

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 278 amino acids

(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

	Pro	Thr	Leu	Leu	Ile	Gly	Ser	Ser	Leu	Gln	Ala	Thr	Cys	Ser	Ile	His	
10	51				55					60						65	
	Gly	Asp	Thr	Pro	Gly	Ala	Thr	Ala	Glu	Gly	Leu	Tyr	Trp	Thr	Leu	Asn	
				70					75						80		
15	Gly	Arg	Arg	Leu	Pro	Ser	Glu	Leu	Ser	Arg	Leu	Leu	Asn	Thr	Ser	Thr	
		85						90					95				
	Leu	Ala	Leu	Ala	Leu	Ala	Asn	Leu	Asn	Gly	Ser	Arg	Gln	Gln	Ser	Gly	
	100						105						110				
20	Asp	Asn	Leu	Val	Cys	His	Ala	Arg	Asp	Gly	Ser	Ile	Leu	Ala	Gly	Ser	
	115					120					125					130	
	Cys	Leu	Tyr	Val	Gly	Leu	Pro	Pro	Glu	Lys	Pro	Phe	Asn	Ile	Ser	Cys	
25				135						140						145	
	Trp	Ser	Arg	Asn	Met	Lys	Asp	Leu	Thr	Cys	Arg	Trp	Thr	Pro	Gly	Ala	
				150						155					200		
30	His	Gly	Glu	Thr	Phe	Leu	His	Thr	Asn	Tyr	Ser	Leu	Lys	Tyr	Lys	Leu	
		205						210					215				
	Arg	Trp	Tyr	Gly	Gln	Asp	Asn	Thr	Cys	Glu	Glu	Tyr	His	Thr	Val	Gly	
	220						225					230					
35	Pro	His	Ser	Cys	His	Ile	Pro	Lys	Asp	Leu	Ala	Leu	Phe	Thr	Pro	Tyr	
	235					240					245					250	

Glu Ile Trp Val Glu Ala Thr Asn Arg Leu Gly Ser Ala Arg Ser Asp
 255 260 265
 Val Leu Thr Leu Asp Val Leu Asp Val Val Thr Thr Asp Pro Pro Pro
 5 270 275 280
 Asp Val His Val Ser Arg Val Gly Gly Leu Glu Asp Gln Leu Ser Val
 285 290 295
 Arg Trp Val Ser Pro Pro Ala Leu Lys Asp Phe Leu Phe Gln Ala Lys
 10 300 305 310
 Tyr Gln Ile Arg Tyr Arg Val Glu Asp Ser Val Asp Trp Lys Val Val
 315 320 325 330
 15 Asp Asp Val Ser Asn Gln Thr Ser Cys Arg Leu Ala Gly Leu Lys Pro
 335 340 345
 Gly Thr Val Tyr Phe Val Gln Val Arg Cys Asn Pro Phe Gly Ile Tyr
 20 350 355 360
 Gly Ser Lys Lys Ala Gly
 365

25

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 143 base pairs
 (B) TYPE: nucleic acids
 (D) TOPOLOGY: linear

30

(ii) MOLECULE TYPE: protein

35

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

GGCATGAAGG CTTAGGGTGG GGATCGGTAG GACCCATGCA CCCAGAGAAA GGGACTGGTG 60

GCAACTTTCA AACTCTCTGG GGAAGGAAGA AGGGCTGAAA GAGG 104

5 ATG AAC GGG CTC AGA CAC AGC TGT AAT CAG CCC CCA GGA 143
Met Asn Gly Leu Arg His Ser Cys Asn Gln Pro Pro Gly
5 10

10 (2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 13 amino acids
(B) TYPE: amino acids
15 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

20

Met Asn Gly Leu Arg His Ser Cys Asn Gln Pro Pro Gly
5 10

25

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

30 (A) LENGTH: 1930 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

35 (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

	GGCACGAGCT TCGCTGTCCG CGCCCAGTGA CGCGCGTGCG GACCCGAGCC CCAATCTGCA	60
5	CCCCGCAGAC TCGCCCCCGC CCCATACCGG CGTTGCAGTC ACCGCCC GTT GCGCGCCACC	120
	CCCAATGCCC GCGGGTCGCC CGGGCCCCGT CGCCCAATCC GCGCGGCGGC CGCCGCGGCC	180
	GCTGTCCTCG CTGTGGTCGC CTCTGTTGCT CTGTGTCCTC GGGGTGCCTC GGGGCGGATC	240
10	GGGAGCCCAC ACAGCTGTAA TCAGCCCCCA GGACCCACAC CTTCTCATCG GTCCTCCCT	300
	GCAAGCTACC TGCTCTATAC ATGGAGACAC ACCTGGGGCC ACCGCTGAGG GGCTCTACTG	360
15	GACCCTCAAT GGTGCGCCGCC TGCCCTCTGA GCTGTCCCGC CTCCTTAACA CCTCCACCCT	420
	GGCCCTGGCC CTGGCTAACC TTAATGGGTC CAGGCAGCAG TCAGGAGACA ATCTGGTGTG	480
	TCACGCCCCGA GACGGCAGCA TTCTGGCTGG CTCCTGCCTC TATGTTGGCT TGCCCCCTGA	540
20	GAAGCCCTTT AACATCAGCT GCTGGTCCCG GAACATGAAG GATCTCACGT GCCGCTGGAC	600
	ACCGGGTGCA CACGGGGAGA CATTCTTACA TACCAACTAC TCCCTCAAGT ACAAGCTGAG	660
25	GTGGTACGGT CAGGATAACA CATGTGAGGA GTACCACACT GTGGGCCCTC ACTCATGCCA	720
	TATCCCCAAG GACCTGGCCC TCTTCACTCC CTATGAGATC TGGGTGGAAG CCACCAATCG	780
	CCTAGGCTCA GCAAGATCTG ATGTCCTCAC ACTGGATGTC CTGGACGTGG TGACCACGGA	840
30	CCCCCACCC GACGTGCACG TGAGCCGCGT TGGGGGCCTG GAGGACCAGC TGAGTGTGCG	900
	CTGGGTCTCA CCACCAGCTC TCAAGGATTT CCTCTTCCAA GCCAAGTACC AGATCCGCTA	960
35	CCGCGTGGAG GACAGCGTGG ACTGGAAGGT GGTGGATGAC GTCAGCAACC AGACCTCCTG	1020
	CCGTCTCGCG GGCCTGAAGC CCGGCACCGT TTA CTTCGTC CAAGTGCGTT GTAACCCATT	1080

CGGGATCTAT GGGTCGAAAA AGGCGGGAAT CTGGAGCGAG TGGAGCCACC CCACCGCTGC 1140

CTCCACCCCT CGAAGTGAGC GCCCGGGCCC GGGCGGCGGG GTGTGCGAGC CGCGGGGCGG 1200

5 CGAGCCCAGC TCGGGCCCCG TCGGGCGCGA GCTCAAGCAG TTCCTCGGCT GGCTCAAGAA 1260

GCACGCATAC TGCTCGAACC TTAGTTTCCG CCTGTACGAC CAGTGGCGTG CTTGGATGCA 1320

GAAGTCACAC AAGACCCGAA ACCAGGTAGG AAAGTTGGGG GAGGCTTGCG TGGGGGGTAA 1380

10 AGGAGCAGAG GAAGAGAGAG ACCCGGGTGA GCAGCCTCCA CAACACCGCA CTCTTCTTTC 1440

CAAGCACAGG ACGAGGGGAT CCTGCCCTCG GGCAGACGGG GTGCGGCGAG AGGTAAGGGG 1500

15 GTCTGGGTGA GTGGGGCCTA CAGCAGTCTA GATGAGGCCC TTTCCCCTCC TTCGGTGTTG 1560

CTCAAAGGGA TCTCTTAGTG CTCATTTTAC CCACTGCAAA GAGCCCCAGG TTTTACTGCA 1620

TCATCAAGTT GCTGAAGGGT CCAGGCTTAA TGTGGCCTCT TTTCTGCCCT CAGGTCTTGC 1680

20 CGGCTAAACT CTAAGGATAG GCCATCCTCC TGCTGGGTCA GACCTGGAGG CTCACCTGAA 1740

TTGGAGCCCC TCTGTACCTA TCTGGGCAAC AAAGAAACCT ACCATGAGGC TGGGGCACAA 1800

25 TGAGCTCCCA CAACCACAGC TTTGGTCCAC ATGATGGTCA CACTTGGATA TACCCAGTG 1860

TGGGTAAGGT TGGGGTATTG CAGGGCCTCC CAACAATCTC TTAAATAAAA TAAAGGAGTT 1920

30 GTTCAGGTAA 1930

(2) INFORMATION FOR SEQ ID NO:23:

- 35 (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 560 base pairs
 - (B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

10	TCCAGGCAGC GGTCGGGGGA CAACCTCGTG TGCCACGCCC GTGACGGCAG CATCCTGGCT	60
	GGCTCCTGCC TCTATGTTGG CCTGCCCCCA GAGAAACCCG TCAACATCAG CTGCTGGTCC	120
	AAGAACATGA AGGACTTGAC CTGCCGCTGG ACGCCAGGGG CCCACGGGGA GACCTTCCTC	180
15	CACACCAACT ACTCCCTCAA GTACAAGCTT AGGTGGTATG GCCAGGACAA CACATGTGAG	240
	GAGTACCACA CAGTGGGGCC CCACTCCTGC CACATCCCCA AGGACCTGGC TCTCTTTACG	300
20	CCCTATGAGA TCTGGGTGGA GGCCACCAAC CGCCTGGGCT CTGCCCGCTC CGATGTACTC	360
	ACGCTGGATA TCCTGGATGT GGTGACCACG GACCCCCCGC CCGACGTGCA CGTGAGCCGC	420
	GTCGGGGGCC TGGAGGACCA GCTGAGCGTG CGCTGGGTGT CGCCACCCGC CCTCAAGGAT	480
25	TTCCTTTTTC AAGCCAAATA CCAGATCCGC TACCGAGTGG AGGACAGTGT GGAATGGAAG	540
	GTGGTGGACG ATGTGAGCAA	560

30

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1391 base pairs

35

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(ix) FEATURE:

5 (A) NAME/KEY: CDS
(B) LOCATION: 1..1053

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

10 ACC CTC AAC GGG CGC CGC CTG CCC CCT GAG CTC TCC CGT GTA CTC AAC 48
Thr Leu Asn Gly Arg Arg Leu Pro Pro Glu Leu Ser Arg Val Leu Asn
1 5 10 15

15 GCC TCC ACC TTG GCT CTG GCC CTG GCC AAC CTC AAT GGG TCC AGG CAG 96
Ala Ser Thr Leu Ala Leu Ala Leu Ala Asn Leu Asn Gly Ser Arg Gln
20 25 30

CGG TCG GGG GAC AAC CTC GTG TGC CAC GCC CGT GAC GGC AGC ATC CTG 144
20 Arg Ser Gly Asp Asn Leu Val Cys His Ala Arg Asp Gly Ser Ile Leu
35 40 45

GCT GGC TCC TGC CTC TAT GTT GGC CTG CCC CCA GAG AAA CCC GTC AAC 192
Ala Gly Ser Cys Leu Tyr Val Gly Leu Pro Pro Glu Lys Pro Val Asn
25 50 55 60

ATC AGC TGC TGG TCC AAG AAC ATG AAG GAC TTG ACC TGC CGC TGG ACG 240
Ile Ser Cys Trp Ser Lys Asn Met Lys Asp Leu Thr Cys Arg Trp Thr
65 70 75 80

30 CCA GGG GCC CAC GGG GAG ACC TTC CTC CAC ACC AAC TAC TCC CTC AAG 288
Pro Gly Ala His Gly Glu Thr Phe Leu His Thr Asn Tyr Ser Leu Lys
85 90 95

35 TAC AAG CTT AGG TGG TAT GGC CAG GAC AAC ACA TGT GAG GAG TAC CAC 336
Tyr Lys Leu Arg Trp Tyr Gly Gln Asp Asn Thr Cys Glu Glu Tyr His
100 105 110

	ACA GTG GGG CCC CAC TCC TGC CAC ATC CCC AAG GAC CTG GCT CTC TTT	384
	Thr Val Gly Pro His Ser Cys His Ile Pro Lys Asp Leu Ala Leu Phe	
	115 120 125	
5	ACG CCC TAT GAG ATC TGG GTG GAG GCC ACC AAC CGC CTG GGC TCT GCC	432
	Thr Pro Tyr Glu Ile Trp Val Glu Ala Thr Asn Arg Leu Gly Ser Ala	
	130 135 140	
10	CGC TCC GAT GTA CTC ACG CTG GAT ATC CTG GAT GTG GTG ACC ACG GAC	480
	Arg Ser Asp Val Leu Thr Leu Asp Ile Leu Asp Val Val Thr Thr Asp	
	145 150 155 160	
15	CCC CCG CCC GAC GTG CAC GTG AGC CGC GTC GGG GGC CTG GAG GAC CAG	528
	Pro Pro Pro Asp Val His Val Ser Arg Val Gly Gly Leu Glu Asp Gln	
	165 170 175	
20	CTG AGC GTG CGC TGG GTG TCG CCA CCC GCC CTC AAG GAT TTC CTC TTT	576
	Leu Ser Val Arg Trp Val Ser Pro Pro Ala Leu Lys Asp Phe Leu Phe	
	180 185 190	
25	CAA GCC AAA TAC CAG ATC CGC TAC CGA GTG GAG GAC AGT GTG GAC TGG	624
	Gln Ala Lys Tyr Gln Ile Arg Tyr Arg Val Glu Asp Ser Val Asp Trp	
	195 200 205	
30	AAG GTG GTG GAC GAT GTG AGC AAC CAG ACC TCC TGC CGC CTG GCC GGC	672
	Lys Val Val Asp Asp Val Ser Asn Gln Thr Ser Cys Arg Leu Ala Gly	
	210 215 220	
35	CTG AAA CCC GGC ACC GTG TAC TTC GTG CAA GTG CGC TGC AAC CCC TTT	720
	Leu Lys Pro Gly Thr Val Tyr Phe Val Gln Val Arg Cys Asn Pro Phe	
	225 230 235 240	
40	GGC ATC TAT GGC TCC AAG AAA GCC GGG ATC TGG AGT GAG TGG AGC CAC	768
	Gly Ile Tyr Gly Ser Lys Lys Ala Gly Ile Trp Ser Glu Trp Ser His	
	245 250 255	

CCC ACA GCC GCC TCC ACT CCC CGC AGT GAG CGC CCG GGC CCG GGC GGC 816
 Pro Thr Ala Ala Ser Thr Pro Arg Ser Glu Arg Pro Gly Pro Gly Gly
 260 265 270

5 GGG GCG TGC GAA CCG CGG GGC GGA GAG CCG AGC TCG GGG CCG GTG CGG 864
 Gly Ala Cys Glu Pro Arg Gly Gly Glu Pro Ser Ser Gly Pro Val Arg
 275 280 285

0 CGC GAG CTC AAG CAG TTC CTG GGC TGG CTC AAG AAG CAC GCG TAC TGC 912
 Arg Glu Leu Lys Gln Phe Leu Gly Trp Leu Lys Lys His Ala Tyr Cys
 290 295 300

TCC AAC CTC AGC TTC CGC CTC TAC GAC CAG TGG CGA GCC TGG ATG CAG 960
 Ser Asn Leu Ser Phe Arg Leu Tyr Asp Gln Trp Arg Ala Trp Met Gln
 5 305 310 315 320

AAG TCG CAC AAG ACC CGC AAC CAG CAC AGG ACG AGG GGA TCC TGC CCT 1008
 Lys Ser His Lys Thr Arg Asn Gln His Arg Thr Arg Gly Ser Cys Pro
 325 330 335

0 CGG GCA GAC GGG GCA CGG CGA GAG GTC CTG CCA GAT AAG CTG TAGGGGCTCA 1060
 Arg Ala Asp Gly Ala Arg Arg Glu Val Leu Pro Asp Lys Leu
 340 345 350

5 GGCCACCCTC CCTGCCACGT GGAGACGCAG AGGCCGAACC CAAACTGGGG CCACCTCTGT 1120

ACCCTCACTT CAGGGCACCT GAGCCCCTCA GCAGGAGCTG GGGTGGCCCC TGAGCTCCAA 1180

CGGCCATAAC AGCTCTGACT CCCACGTGAG GCCACCTTTG GGTGCACCCC AGTGGGTGTG 1240

0 TGTGTGTGTG TGAGGGTTGG TTGAGTTGCC TAGAACCCTT GCCAGGGCTG GGGGTGAGAA 1300

GGGGAGTCAT TACTCCCCAT TACCTAGGGC CCCTCCAAAA GAGTCCTTTT AAATAAATGA 1360

5 GCTATTTAGG TGCAAAAAA AAAAAAAAAA A 1391

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 350 amino acids
 (B) TYPE: amino acid
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

```

    Thr Leu Asn Gly Arg Arg Leu Pro Pro Glu Leu Ser Arg Val Leu Asn
      1             5             10             15

15    Ala Ser Thr Leu Ala Leu Ala Leu Ala Asn Leu Asn Gly Ser Arg Gln
           20             25             30

    Arg Ser Gly Asp Asn Leu Val Cys His Ala Arg Asp Gly Ser Ile Leu
           35             40             45

20    Ala Gly Ser Cys Leu Tyr Val Gly Leu Pro Pro Glu Lys Pro Val Asn
           50             55             60

    Ile Ser Cys Trp Ser Lys Asn Met Lys Asp Leu Thr Cys Arg Trp Thr
25    65             70             75             80

    Pro Gly Ala His Gly Glu Thr Phe Leu His Thr Asn Tyr Ser Leu Lys
           85             90             95

30    Tyr Lys Leu Arg Trp Tyr Gly Gln Asp Asn Thr Cys Glu Glu Tyr His
           100            105            110

    Thr Val Gly Pro His Ser Cys His Ile Pro Lys Asp Leu Ala Leu Phe
           115            120            125

35    Thr Pro Tyr Glu Ile Trp Val Glu Ala Thr Asn Arg Leu Gly Ser Ala
           130            135            140

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	Arg Ser Asp Val Leu Thr Leu Asp Ile Leu Asp Val Val Thr Thr Asp	
	145	150 155 160
5	Pro Pro Pro Asp Val His Val Ser Arg Val Gly Gly Leu Glu Asp Gln	
	165	170 175
	Leu Ser Val Arg Trp Val Ser Pro Pro Ala Leu Lys Asp Phe Leu Phe	
	180	185 190
10	Gln Ala Lys Tyr Gln Ile Arg Tyr Arg Val Glu Asp Ser Val Asp Trp	
	195	200 205
	Lys Val Val Asp Asp Val Ser Asn Gln Thr Ser Cys Arg Leu Ala Gly	
	210	215 220
15	Leu Lys Pro Gly Thr Val Tyr Phe Val Gln Val Arg Cys Asn Pro Phe	
	225	230 235 240
	Gly Ile Tyr Gly Ser Lys Lys Ala Gly Ile Trp Ser Glu Trp Ser His	
20	245	250 255
	Pro Thr Ala Ala Ser Thr Pro Arg Ser Glu Arg Pro Gly Pro Gly Gly	
	260	265 270
25	Gly Ala Cys Glu Pro Arg Gly Gly Glu Pro Ser Ser Gly Pro Val Arg	
	275	280 285
	Arg Glu Leu Lys Gln Phe Leu Gly Trp Leu Lys Lys His Ala Tyr Cys	
	290	295 300
30	Ser Asn Leu Ser Phe Arg Leu Tyr Asp Gln Trp Arg Ala Trp Met Gln	
	305	310 315 320
	Lys Ser His Lys Thr Arg Asn Gln His Arg Thr Arg Gly Ser Cys Pro	
35	325	330 335

Arg Ala Asp Gly Ala Arg Arg Glu Val Leu Pro Asp Lys Leu
340 345 350

5 (2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

TCCAGGCAGC GGTCGGGGGA CAAC

24

20

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

- 25 (A) LENGTH: 24 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

30 (ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

35 TTGCTCACAT CGTCCACCAC CTTC

24

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:

- 5 (A) LENGTH: 6663 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

15 CCCAGAACTC TTGGACGCTG AGGCAGGAGG ATTCCCAAGT TTCAAGACAG TGTGTTTCTA 60
GGTAATGAGA CCCTGTCAAG AAAAGAAAAG AAATAAAGAG ACAAGAAAAT GTTTATAGGC 120
TGTGAGACAG CTTGGTGGGT AAGGGGCACT TGCCTCCAAT CAAGATGACC TCAGCCCCAT 180
20 CCCTAGGAAT CCATGGTAGA AGGAGAAAGC AAATCGCAG CTGCTGACCT CCATACATGT 240
GCTCCAATGT GCACACACAC AGGGAGACAT AATCAATTAA TAGGATGTAT TTGCTTAGAT 300
25 TTGAGTAGGC ATTTATGACT GATGTTTTAA AATTTTTATT TGATTTTATG AAAATATAACC 360
TGTTTGTATT TGGTTTGTT TGGTTTGAGT TTTGTTTATT TGAGACAGGG CTTCTCTGTG 420
TAGTCCTGGC TGTCCTTGGA ACTCACTCTG TAGACCAGGC TGGCCTTGAA CTCAGAAATC 480
30 CGCCTGCTTG TGCTTCCCAA GTGCTTAGAT TAAAGGTGTG CACTGCCATT CAGCAAAATT 540
GCATACTTTA ACCCCAGTAT TTGGGAGGCA GAGGCAGACT AATGTGTGAA TTCCAGGCTA 600
35 GCCAAGGATA CAGAGTGAGA CCCTATTCTT ACCCTCCCCC CCCAAAACCC CAAAATGTAT 660
TTTGTGCTTG TGTATGTACA TGTGTGTTGC AGCACGTAAA TGTCCAAGGA CAACTTGTAG 720

	AAGTTCTCTC CGTTCACAGT CTAAGTCCTG AATTCAAACT AAGGTCCTCA GGCTTAGCCA	780
	CAGTCTTCTT TATGTACTGA GCCATTTAC TGGCCCTGGA TTGACTGATG AATTAATTTT	840
5	TGAGATAAGG TCTCTTGTAG CTCTAGCTAG GCTCAAATA TGAAGTCCCA AGGTCATCTT	900
	GAGCTGCTGG TACTCTTGCT TCCACCCCCA GTGGTGGAAT GATACTCAGG CAGCACTTCT	960
	CTGGGGAAGG GGCTGGCCTT GGCCTTGATT TTGTTGCCTC AGCTTCAATG AGTGCTTGGG	1020
10	TCTCGTTGTT TCTTTTCTTT ATCTGTGAAA TGGGTGAACA CCTGTTCAAG ACTTCCTGAC	1080
	TCTTGAAACA TCCAGGCAGG GTGAGGGACT TGAAGTGGGC TCATCCCATG CCTAACAAAG	1140
15	TGTCGTCTTT GACCCAGAC ACAGCTGTAA TCAGCCCCCA GGACCCACC CTTCTCATCG	1200
	GCTCCTCCCT GCAAGCTACC TGCTCTATAC ATGGAGACAC ACCTGGGGCC ACCGCTGAGG	1260
	GGCTCTACTG GACCTTCAAT GGTCGCCGCC TGCCCTCTGA GCTGTCCCGC CTCCTTAACA	1320
20	CCTCCACCCT GGCCCTGGCC CTGGCTAACC TTAATGGGTC CAGGCAGCAG TCAGGAGACA	1380
	ATCTGGTGTG TCACGCCCGA GACGGCAGCA TTCTGGCTGG CTCCTGCCTC TATGTTGGCT	1440
25	GTAAGTGGGG CCCCAGACAC TCAGAGATAG ATGGGGGTTG GCAATGACAG ATTTAGAGCC	1500
	TGGGTCTTCT GTCCTGGGGC AGAGCCATGG GCTCTCACTT GCATGCAGGC ATGGTCATAC	1560
	CCAGCACAGG CATTGCAACT CTAGGGACAG CTGTGGCTGC ACTGTCCCCT GTGTACCCCA	1620
30	CAGCTTTAGA AAAGCTGTCA TGTTTTCTTT GTAGTGCCCC CTGAGAAGCC CTTTAACATC	1680
	AGCTGCTGGT CCCGGAACAT GAAGGATCTC ACGTGCCGCT GGACACCGGG TGCACACGGG	1740
35	GAGACATTCT TACATACCAA CTAATCCCTC AAGTACAAGC TGAGGTTGGT ACCCAGCCAA	1800
	GCCTTGCTGT GTGACTTCTG GCAATACTTA CCTTCTCTGA TCAAATATGT TCCTGTTTAT	1860

GAACTCAAAA GGGACTCTCG CACCTCCACA GGTGGTACGG TCAGGATAAC ACATGTGAGG 1920

AGTACCACAC TGTGGGCCCT CACTCATGCC ATATCCCCAA GGACCTGGCC CTCTTCACTC 1980

5 CCTATGAGAT CTGGGTGGAA GCCACCAATC GCCTAGGCTC AGCAAGATCT GATGTCCTCA 2040

CACTGGATGT CCTGGACGTG GGTGAGCCCC CAGTGTCCAC CTGTGTTCTG CCCTAGACCT 2100

TATAGGGCGC CTCCCCCCCC TCCCCCAGA CTTTTTGGTT CTTCTAGAGG TCTTAGCCAC 2160

10 AGCCACGGTG GTTGCAGGAC AGTGGTTGTT CATAACTTAA TGCAAAGACT TTCCCCAAG 2220

ACAGTCAAGA TTTTTCCTCT CCCCACCCCC AACACACACA TACACACACA CTCTGCAGAG 2280

15 AACACCTGGC CTGACCACCC TCCCTCTCTA CAGCCCAGGT GTTCAGAAGG GAGTCCTAGG 2340

GGACTGAGAG GAGGCGCCCA GGTCTGAAGG CGCCCCAGGA AGCCGAGGCC TTGAGCTGGG 2400

GGGGGGGGCG AGGGTTGGAG GCACGAACTG GATGATCCCT GAGCACAACCT GGGCCTAATC 2460

20 TAATTAGGGT GTTCCCAGCC CAAAGCAGCC TGGGCCATTT AACCCCTCAA GTGCCTCACT 2520

GAAGACTCAG GGGAGAGATC AGCTTGTA CTCTCCATGG TCCCCAGGA GGGTTCCTGG 2580

25 GTGCCCCTGG CTCATTCCCA CATCCAGAGG TTTTGTGTCT TCCTGGCATC TAACCCTCAG 2640

TTGTGCTCTG TGGCTGGCAC AGCTGCCCCG TGGAGGCTCT TGGTAATGTA CAAGGCATCA 2700

GAGGTGGACA TGGGATGGGG ATACATAGGG ATGGAGCCAA ATAGCACCTC AAGGTGGGGT 2760

30 GATATACAAT AAAGCTTGTC ACCCTGACGC TCAGAAAGCC TACTCATGAT GATCACAATT 2820

GTTGACATCA CTCTGGGACA TGTAGTGAGA CCCTAGCTCA AAACACAGAC AGTAGCTTTA 2880

35 AGAGTCAGCT TGTGACTTAA TACTGGAAC CAGGGCCTAA TAGGTGCTGG GTGATGCTCG 2940

CCTCACTCCC TGTTTAGTGA GATCTCTGCG CTAATCTCCA CCCCAGCTGG GTGGGCTGCT 3000

CTGTCCCCTT GAGGGCAGGA ATGTGTGTCT TCCATCAGAG ATAGGACCCG TGGTAGCAGC 3060

AACTGCTGCT GGCTGTTTCT GGAATATTAA ATGACAGTAA TCTATCAGGC CTGGGTGAGT 3120

5 AGCTAACAGG GGTGGGGGCG TGGTCTGGAA AACGCAGATA GGGTCATAGG AGCCACTGCA 3180

GCCTAGATTA CACCACTGGG TGTTCGTCA CTAGGCCATT CTCACCAAGC AGTCCTCAGA 3240

ACTGGGAGCA CTGTTGCCAG CATTTAATGC CAGCATTTAA TGCCAGCATT AGGGGAGGCA 3300

10 GAGGCAGAAG GATCTCTCTG AGTTCAAGGC CATCCTGAAT TTACATAAAG AGCTCCAGGC 3360

CAGCCAGGGT GCGCAGTAAA ACCTTGTCTC AAAAAACAAA GCATCTTTAG TGACCAGGCT 3420

15 TGCTCCACCC CCAGTGACCA CGGACCCCCC ACCCGACGTG CACGTGAGCC GCGTTGGGGG 3480

CCTGGAGGAC CAGCTGAGTG TGCCTGGGT CTCACCACCA GCTCTCAAGG ATTCCTCTT 3540

CCAAGCCAAG TACCAGATCC GCTACCGCGT GGAGGACAGC GTGGACTGGA AGGTGCCCGT 3600

20 CCGGCCCCGG ACCCGCCCCT GACCCGCCCC CCCGCATCTG ACTCCTCCCT CACCGTGCAG 3660

GTGGTGGATG ACGTCAGCAA CCAGACCTCC TGCCGTCTCG CGGGCCTGAA GCGCGGCACC 3720

25 GTTTACTTCG TCCAAGTGCG TTGTAACCCA TTCGGGATCT ATGGGTCGAA AAAGGCGGGA 3780

ATCTGGAGCG AGTGGAGCCA CCCCACCGCT GCCTCCACCC CTCGAAGTGG TGAGCACCTC 3840

TCCAGGGCTG GCTGGCCCAT GGAATCCCCA ATCCATCCTG TTCCTTCCCC CCCACCCTTT 3900

30 TTTTGAGACA GCGTCTTCAG GTAGCGCATG CTGGCCTTAA ATTCAGTATG TAGTCAAGGA 3960

TGACCTCGAG CTCCTGGTCT TTTTGTCTCC ACTTAGAGAC AATGGCCAGT GGCCATCACC 4020

35 ACCTTTGGGA GACTAGCCAT GGAGTCTATT TAGCCTGTCA TTTGGTGACA GATGGAGTAC 4080

AACAGTGTGA CCTCTTGTA GAGAACTGAA GACAGGCTGT TTTTAACCCC AATATCCTAG 4140

GCTCTCTAGA GGTAACTTT ATATAAAATA GAGACTATTA CAGCCAGTTA TCACATGGTC 4200

CCACAGAACC TTTTGTACA CAACCTATAG ACCACAGTGC CTGTGCCTAC CACATAAGGG 4260

5 TCTCTACTGC TGGCCACCC CTCCAACCCT TAAAAGGTAA CCTAGGCAGC CTTAATATTT 4320

GCAATCCTCC TACCTCAGCC TCTTGAATGC TCAGAAACCA GGCATTAACC CAAGTTTCTC 4380

10 TTCTCTGGGT CCCTTTCTTA AGGTGGGAGG GCCTAAAGAT GACTTCCTTT GTCCTGAAGA 4440

CTCTCCGAGC CCATGGATCT GCACTCTCTA ATATGAAATA TATTGCATAA AATGTCTGGC 4500

CTCAGTTTCC CCACCTGTCA GGTTTAGGCA GCACAGTCGG TCCAAGACAC TTCATTATTT 4560

15 GCAGGCAGTA TAAGAAGAAG CTCCCATCCC CCACCCGCTT CCTCCGGTCC CTAAGACAGA 4620

ATACTTCTAC ACTGAACTG AACTCTCGCA GACGCATATG CTCACTTTAA TGATGATGAA 4680

ATAATGGGGA AACTGAGGCT CCGAGAGATT CCTGGAGGAA GAGGGTCAAA ACCAGCTCCA 4740

20 GGAAGCTCTC CAGCCCCCAT CCGGGCCTCT CCAGGTTCTG GGCTTGCGG GAGTGAACAC 4800

AGCTGGGAGG GGCTGGAGCC TGGGAGCTTT GGCCCTTGCT CGTGCCAGC ACCTGCGATT 4860

25 CTTGCACGGG AGCCAGCAGG CGGCTGCGTC CGCCGAGAG ACTGAAGAAG CCGGGGGTAG 4920

GGTTGGAGGG AGGTAAGCAG GGGCTGTGGG GGCCGAAGCT TGTGCCAGGG CCTGTCAGCG 4980

AGTCCCCAGT TTTATTTATG GCGTGAGGCC GATGTCCTTA TCCGCTGGCC TGCTGGGGGA 5040

30 TGGCTGCGGC TGGGGATTGG ACCCAAGGGC TGGCTTCCCA CTCAGTCCTC CAGCCCCTC 5100

CATGTCACAC CCGTGCATTG TCTGAGGCTT ATCTTGGGAA CCCGCCCTTG TTCTGTGCTG 5160

35 TCTGTCTCTA TTTCTGTCAT TCACTTTCCC AGAGCCTTTT TTTTATGCTT TTAATATAAC 5220

TACGTTTTAA AAATTGCTTT TGTATAATGT GTGTGCCTTC GTGAGCGTGC GTGCCACAAC 5280

ACACACGTGA AGGTTAGAGA ACTTTGTTGA GTAGGCTCCT TCCACCATGT GGGACTAGGG 5340

CTGGCGACAA GAGCAATTAC TGAGTCATCT CGCCAGCCCC TCACCCCTCA CTTCCCATCC 5400

5 TGT TTGGATA GTCATAGGTA ATCGAAGGTA AATCGCTGGC TTTAATTTTCG TAGCTATCCT 5460

GCCTCAGCCT ACCAAGTGCT GTGCTACCAC GTTTGTGGGA GGGGCTCTCC TCCCAGTGTC 5520

TGGGGGTGAC ACAGTCCCAA GATCTCTGCT TTCTAGGTCT TTGTCTTAGT TTGCCCCCTG 5580

10 CTTTGTCCGT GTCCCTAGAG TCTCCGGCCC CACTTATCCA TTGACTGGTC TTTCCCTTAC 5640

CGAATACTCG GTTTTACCTC CCACTGATTT GACTCCCTCC TTTGCTTGTC TCCATCGCCG 5700

15 TGGCATTGCC ATTCCTCTGG GTGACTCTGG GTCCACACCT GACACCTTTC CCAACTTTCC 5760

CCAGCCGAAG CTGGTCTGGT ATGGGAGGCC GCCGTCCCGC GCGCGCCTCC TGCTGGCCGC 5820

GCCCCAACAC TGCCGCTCCA TTCTCTTTAG AGCGCCCGGG CCCGGGCGGC GGGGTGTGCG 5880

20 AGCCGCGGGG CGGCGAGCCC AGCTCGGGCC CGGTGCGGCG CGAGCTCAAG CAGTTCCTCG 5940

GCTGGCTCAA GAAGCACGCA TACTGCTCGA ACCTTAGTTT CCGCCTGTAC GACCAGTGGC 6000

25 GTGCTTGAT GCAGAAGTCA CACAAGACCC GAAACCAGGT AGGAAAGTTG GGGGAGGCTT 6060

GCGTGGGGGG TAAAGGAGCA GAGGAAGAGA GAGACCCGGG TGAGCAGCCT CCACAACACC 6120

GCACTCTTCT TTCCAAGCAC AGGACGAGGG GATCCTGCCC TCGGGCAGAC GGGGTGCGGC 6180

30 GAGAGGTAAG GGGGTCTGGG TGAGTGGGGC CTACAGCAGT CTAGATGAGG CCCTTTCCCC 6240

TCCTTCGGTG TTGCTCAAAG GGATCTCTTA GTGCTCATTT CACCCACTGC AAAGAGCCCC 6300

35 AGGTTTTACT GCATCATCAA GTTGCTGAAG GGTCCAGGCT TAATGTGGCC TCTTTTCTGC 6360

CCTCAGGTCC TGCCGGCTAA ACTCTAAGGA TAGGCCATCC TCCTGCTGGG TCAGACCTGG 6420

AGGCTCACCT GAATTGGAGC CCCTCTGTAC CATCTGGGCA ACAAAGAAAC CTACCAGAGG 6480

CTGGGCACAA TGAGCTCCCA CAACCACAGC TTTGGTCCAC ATGATGGTCA CACTTGGATA 6540

5 TACCCAGTG TGGGTAGGGT TGGGGTATTG CAGGGCCTCC CAAGAGTCTC TTAAATAAA 6600

TAAAGGAGTT GTTCAGGTCC CGATGGCCAG TGTGTTTGGG GCCTATGTGC TGGGGTGGGG 6660

GGA 6663

10

(2) INFORMATION FOR SEQ ID NO:29:

15

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 186 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

20

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

25 Asp Pro Thr Leu Leu Ile Gly Ser Ser Leu Gln Ala Thr Cys Ser Ile
 1 5 10 15

His Gly Asp Thr Pro Gly Ala Thr Ala Glu Gly Leu Tyr Trp Thr Phe
 20 25 30

30 Asn Gly Arg Arg Leu Pro Ser Glu Leu Ser Arg Leu Leu Asn Thr Ser
 35 40 45

Thr Leu Ala Leu Ala Leu Ala Asn Leu Asn Gly Ser Arg Gln Gln Ser
 35 50 55 60

Gly Asp Asn Leu Val Cys His Ala Arg Asp Gly Ser Ile Leu Ala Gly
 65 70 75 80
 Ser Cys Leu Tyr Val Gly Leu Pro Pro Glu Lys Pro Phe Asn Ile Ser
 5 85 90 95
 Cys Trp Ser Arg Asn Met Lys Asp Leu Thr Cys Arg Trp Thr Pro Gly
 100 105 110
 Ala His Gly Glu Thr Phe Leu His Thr Asn Tyr Ser Leu Lys Tyr Lys
 115 120 125
 Leu Arg Leu Val Arg Ser Gly * His Met * Gly Val Pro His Cys
 130 135 140
 Gly Pro Ser Leu Met Pro Tyr Pro Gln Gly Pro Gly Pro Leu His Ser
 145 150 155 160
 Leu * Asp Leu Gly Gly Ser His Gln Ser Pro Arg Leu Ser Lys Ile
 165 170 175
 * Cys Pro His Thr Gly Cys Pro Gly Arg
 180 185

25

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 35 base pairs
 (B) TYPE: nucleic acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

30

(ii) MOLECULE TYPE: DNA

35

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

AGCTGGCGCG CCTCCCGGGC GGATCGGGAG CCCAC

35

5 (2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

20 AGCTACGCGT TTAGAGTTTA GCCGGCAG

28

(2) INFORMATION FOR SEQ ID NO:32:

25 (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 30 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

30

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

35

Met Val Leu Ala Ser Ser Thr Thr Ser Ile His Thr Met Leu Leu Leu
1 5 10 15

Leu Leu Met Leu Phe His Leu Gly Leu Gln Ala Ser Ile Ser
20 25 30

5

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

- 10 (A) LENGTH: 30 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

15

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

20

Ile Lys Pro Ser Gly Arg Arg Gly Ala Ala Arg Gly Pro Ala Gly Asp Tyr Lys Asp Asp
5 10 15 20
Asp Asp Lys

25

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:

- 30 (A) LENGTH: 73 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

35

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

5 GATCTTGCCC TCGGGCAGAC GGGGTGCGGC GAGAGGTCCT GCCGGCGACT ACAAGGACGA 60
CGATGACAAG TAG 73

10 (2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 73 base pairs
(B) TYPE: nucleic acid
15 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

25

AACGGGAGCC CGTCTGCCCC ACGCCGCTCT CCAGGACGGC CGCTGATGTT CCTGCTGCTA 60
CTGTTTCATCC TAG 73

30

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 27 base pairs
35 (B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

CCCACGCTTC TCATCGGATT CTCCTG

27

10 (2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 27 base pairs

(B) TYPE: nucleic acid

15 (C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

20

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

25

CAGTCCACAC TGTCTCCAC TCGGTAG

27

30 (2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 11832 base pairs

(B) TYPE: nucleic acid

(C) STRANDEDNESS: single

35 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

	GCGGCCGCTG CAGTGATTAC TCACCGCGTG GCGCACCCCA CCCGCGGGCC GCTGAGTGGA	60
5	TTTTTCCGTG GGGGATGTG AAGAAGTTTA GGGAGAACTC TTCTGCACCG ATGGGAACTA	120
	GGAATGCAGG GTTCGGTCCC GTTCCCCAAA GGACACACCT CTCCCCATAA GCCCACTCAT	180
10	AAGGGCTCCC TGCACGCGCT CCGGGACATC CCCATATCCA ATACCCGCAG ATATGATAGT	240
	TGAGAAGGGA CCAGAGGCCG GAGACTCCCT CCCTGCCTTC TGGCTTTCCC CCCCCCTGC	300
	ACGAAACGAG ACTACAGCGA TGGGAGAGGT GGCATGAAGG CTTAGGGTGG GGATCGGTAG	360
15	GACCCATGCA CCCAGAGAAA GGGACTGGTG GCAACTTTCA AACTCTCTGG GGAAGGAAGA	420
	AGGGCTGAAA GAGGATGAAC GGGCTCAGGT ACTGCTCAAT GTGTGTGTGG CGGACCAAAG	480
	TGGGTATGGG GGCCCCGTAA GAGGGGCGGG GAAGGTGGAT AGGAAGGATC CCGGTAGACT	540
20	GGAGGGGATC CTGGAAAAGC ACCAGGGCTG CGAGCTAGGA ACCCATTCGG AGTTAAGGGT	600
	ACAGGATCCC AGATGAGGGG GTGGGAAGCC TGGGACGGGC GGGACCAGAG AGGGAGGTCC	660
25	CACGGGCTGG TGGGGAAAGA GTGGGGGGCT TCGCGCAGGA GGATGGGACG TTCAGGAGTG	720
	GTAAGTGGGC GGAGGCCGGC CGGGCGGGGC GCGCGGTGCC CGCGGGCGGT GGGGAAGGCCG	780
	GTGCGGGGCC CACGATCAAC CCCCCCCAG GGGCCGGGCC GGGCCGGGGG CGGGGCCGGG	840
30	CGGGGCGAGC GCGCATTAG CGCCTTGTC AATTTCGGCTG CTCAGACTTG CTCCGGCCTT	900
	CGCTGTCCGC GCCCAGTGAC GCGCGTGAGG ACCCGAGCCC CAATCTGCAC CCCGCAGACT	960
35	CGCCCCCGCC CCATACCGGC GTTGCAGTCA CCGCCCGTTG CGCGCCACCC CCATGCCCCG	1020
	GGGTGCCCCG GGCCCCGTG CCCAATCCGC GCGGCGGGCC CCGCGGCCGC TGTCTCGCT	1080

	GTGGTCGCCT CTGTTGCTCT GTGTCCTCGG GGTGCCTCGG GCGGATCGG GAGCCCGTGA	1140
	GTACCGTGCG CCCTGCTCCC CACCTCCCCA GGGAAGCCGG GATCCGGCGC CCCGGGGGGT	1200
5	AGTCGCGGGG GATGGAAGAA GGGGCGCGAG CGCCACCTGG ACGTCCCGGG AACAAAGGAA	1260
	GGCGGCCCTC GGGGCGCCCT CACCTGTGGG GTCATGGCA CCACCACCCA GCCTCCCAAG	1320
	AGTACCCCGT TATACATCAG AGGCCTCTTA TCTGTATCCC CTTTGCGAGG CTGTCTGGCC	1380
10	AGGCTCAGTT TGAAGGACAT CGCAGTGTCC TGGGACCCCC CTCCTTCAGG GTGCTGGGAC	1440
	GCTTCGGGGC GCACGCCTGT GTCTTGATA TCAGAGCGGA AGGGAAGCCT CCCTGGCCGG	1500
15	GGGCGCACGC TTGGGTGCGT TGGGTGGGT GCTGGCGCAA AGTGGGGTCC CCTCCCCCAT	1560
	GAAGTGATGA TCCCCGGGGG GAGGGTGGGG CGTTATCGTG AGCCCTCCTG TCCGCCTGGC	1620
	ATGCGGCCCC GCGTCCCTCG GGAATTGCCT CTCCGTGGGG TCGGCGCCGC CCCCTCCCCC	1680
20	CTATAGCAGA CTCCATGCTT TGGTATCCTC GAAGTCCTCT CCACTGGTGG GGCTCACAAC	1740
	CGGTCTCATT CAGGCTGCGC TGGGTTGAGA GCCTCTAGCG ACTGAAATTT CGGTGAGGAG	1800
25	CGAGAGCAAG CGTGTCCGGG CACCGCGAGC CCAGACTTCA TTGTCTAAGG GGCACCCAGT	1860
	GGGGGTCAGC TGCCGAGAGA ATCCCACTGT CCCAGGAGGA ACTCCTGGCC TTGAGCCCCC	1920
	ATCACCCAAC GCACACATCC CCGCCAGGAT GCGGTCTCCA CATCCAGACC CTCTCTGGGA	1980
30	CACACCCAAA GACACACAAA AGAGCCCCAC TGGCTTATGT CCCGTCACCC TGCCCTCCGA	2040
	CGCGCGCTGC AGCCCAGATG CGTATTCGCA CACCATCGCG GCGCTCGCAT TCCATCCTCT	2100
35	ACACACACAC ACACACACAC ACACACACAC ACACACACAC ACACACAGAC ACGCACACAC	2160
	ACACGCACGC ACACACACGC ACGCCCGCAC TCGTGGTCCC ACATTTATTT CACAGGGGAG	2220

GCAACACCGG GGTACGCATA TGGTTGAGTG CACTGGAGAT CTTTCCCCAC CACTCTCAGG 2280

ACCCCATCCG GAGACACAGG CCACACCGCA GGGGCACCAC GCTGCGCTGC TGCTCTGGGC 2340

5 TAGTAGTCTT GTGCAGTTTG TCCGCGGTGT CTGTGGACGC CCTCCCGCTC TTGTCAGGGG 2400

ACAGGAACCT AACTCCTGC TTGCCCCAAGG CGGCTGGGCA GGTGATGTGG TGACACCCGG 2460

GACCTTTCCG GGGAGTTGGT GTTGCTGCCA AGCCTGGGTA GTTTTTGAAT GCCACCAATA 2520

10 GCGCTAAGCT TTGTTTCCGG GCGGGCTGCA GAGCAACAGG CGAAGGTGGC GGAGTGGGGG 2580

TGGCGCGTGT GTTTTTTCTT TTAAGGGGGA GAGAAATTAA ATAAGAGGTT CTCACACCTC 2640

15 TGCAATCTGT TTGTACTTAC CGTGTGTCTT AACACCTGAC CAGCCAGCCG GTGGGTCGTA 2700

AAAGTGTATG CAGGTACCAG CGGGACAGGA GATGGGGGCC CCTGGGGTAT GGCTGGGATG 2760

GAGGCCACCT TCCCGTTGGC CTTTCAGGGA ATCTCACACT TTTCCCTTTT AAAACACATG 2820

20 GTGTTCTTTT TAATAACGGC AGCAACTCCG CATTGGGAAA GGGGGAAATA AGCTTGTATA 2880

GGCCCCGGCT TTGTGGAAAG GAGGGGAAGA GGGAAGAAAA AAGGAGGGGT GTCTCCTCCA 2940

25 GGCTTAGGGG GCTGTCAGCT GCTGCTCTGT CTAGCTTGGC ATGTGTGTGC CCCAGTCCCC 3000

AGTGGCTTTG GCCCATTGTT TGTGGAAGCC AAGAGGGAGA CTGGAGTCCT CTATCTCTGG 3060

TACTCCAGAG TCAGGCTTCT CAGTCCGAGC CCAGAGAACG TC'TTCCCTGT TTTATGGAGG 3120

30 GAATCAGGGA AGGGGGTGCC AGGTGGACTA CGTTCTGCTG AGGACTGTAC CAGTCGCTCG 3180

AAGGAGAAAG CTTGGGCTTG CCCCCCTCCC CCCTCAAGCC ACGAAGGGCA GCTGCTAGGC 3240

35 TAGTGTGGTA AAAGGGCATT ACTCCCCAGC CAGGACCCCC CAGAGAGTCC CCTTCCTGGC 3300

CAGACAAATG CTGGGGAGGG ACAGAGGGGT GTGATCATTG CCCAGGAGTG CAGACAGTGG 3360

GGTCCCGGGT CGGGCAGTGC CTCCCACCCT GCTGAGGGGG GCGCCCAGGC AGGAAGCGGT 3420

GGGTGGGCCG GGGTAGAGAC GCTGGCACGT CCCAGTTCAT GCCGAAGGAA TTCTGAATTA 3480

5 GCGGGCGGCT GGCTGCCTGG GACCTCCGGG GCGGCCCCCT GGCCCCCGCC GCTCCGTCTG 3540

GCCTGCTCCT CCTGCTCCTT CGCACGGACG CTGAGACCTC CGCTGAGCCC TGGGACAAGC 3600

CCCAAATGCA ACTGCGATTG CAGGCTTCGC AAGACCCGCC TCCTCCCAAG GCCAAATTTG 3660

10 CCTGGGAGAA GTCATTGAGG GCCCAGACTA GAACCATGTT GGTGCCACCT CATCCATCTG 3720

GGGCATGAAG GACCGTCCAG GGCTGCAGTT TAGCTTCTTA ATAGGAACCT GGGGGTGGGT 3780

15 GCAGCCTCTG TTCTCCGAGC CTCTTTGGAA ATCGGTTTTG TTTTGT TTTT TGT TTTT TCC 3840

AATACTCTTT TCCTCTCATC CCATCCCGGG ACTGTTTTCC TCCCTAAGGG TTGAGAGCCC 3900

TGCAGTCTTC CCTAACCTTT TCTTTGCTTC TACCCAGGG CCTTTGCACA TGGAGTCCCA 3960

20 CCTCTCCCTT TGCCCAACTG GGGCTCCAGC CTTACTGCAT TTGGCTCTTG GTAACGTGCC 4020

CAGGGCCTCT CTGACACACA GGGTTGTAGC CCCAGCTCCC TCTCTTCTCC TCCCCCTTT 4080

25 CTCTTTTGCT TCTGAGACTT AATTTTTTTC TTTTCTTTT TGGCTTTTGT AGACAGGGTT 4140

TCTCTGTACA GCCCTGGCTG CCCTGGCACT CATTCTGTAG ACCAGGCTAG CCTCAAACCTC 4200

ACAAACCTAC CTGCCTCTGC CTTTCCAGTG CTGGCACTAA AGATGTGGGC CACCACAACCT 4260

30 AGTAGTTAAG TGTTTTGCTG TGTCTTTATT CCTATAGTGA CCTCAGTTCC TGGCATATTG 4320

TAGGCGATGG ATGGATGAAT GGATGGATGG ATGGATGGAT GGATGGTTGG ATGGAGCAAG 4380

35 CTTGAATCGT CCTGAGTGAA AAAAGAGACC TCAGAGAACT GAATGGAGTT AGGTTCCCAG 4440

GGCAGCCTGG CCTGCTGGTC TCATGGGAGC TCCCTGTGAA ACTTCCCCCA CACCTCCCAC 4500

CACCCTGCCA TCCTGTGTGG CTGACAAGAA AGGCCAATGG CCAGATGGGG ACACAGACTC 4560

AGGGAAGCTT GGAATATGTT CCCCTCCTCA TATCCTAGGC CTTGTTGTCC CCCTGAGGGC 4620

5 CCAGCCTATG AGTAGGGCAG CTGTGGGCTG CCCTAAGGTT GGGTAGGCAA GAAGGGGGTG 4680

GTCCCTCAGG GTGGGTCACA GGATTGAGGT CATTTCCAAA GTGGCCATCA CAGTGGCCCT 4740

AGGAAATGAT TGTGGAGAGT CAGAACTCCT GTTGGGAGTT GTAGAGGGCC TTGCATGTGG 4800

10 GCTTCTGTGG CTGTCCCTTC TCTTGTGGTC CTTTGCACAG TCCCCTCGTG TGTGCTGGGA 4860

TGTGAGGAGG GCACGGGGAA AATGAAGGCT CAGCCCCTCA GCTTGCCCTT CACGGTTCAC 4920

15 CCAACAGGGC TCACCTCTCC TCTGGACAGG CTCTCACTGT ATGCACAGAT TGGCCTCACA 4980

TTTGATTCCC TTCCTTTGGT CTCCTGGGAT GACAAACATT TACCAGGGTA GGATTTTACA 5040

TTTTAGATAT GTCCATTCTC CAGAAACACA CTGTGAGGT TAGGGTATCA GTGAAAGGAC 5100

20 ACCACCAGGA CAGACAAAGA ATTGGAGAGG AAGGAAATTG GTAAGCCAGG CCATGCTTGA 5160

TGGCTTATGT GTAATCCCAG AACTCTGGAC GCTGAGGCAG GAGGATTCCA AGTTTCAAGA 5220

25 CAGTGTGTTC TAGGTAATGA GACCCTGTCA AGAAAAGAAA AGAAATAAAG AGACAAGAAA 5280

ATGTTTATAG GCTGTGAGAC AGCTTGGTGG GTAAGGGGCA CTTGCCTCCA ATCAAGATGA 5340

CCTCAGCCCC ATCCCTAGGA ATCCATGGTA GAAGGAGAAA GCAAACCTCA GCTGCTGACC 5400

30 TCCATACATG TGCTCCAATG TGCACACACA CAGGGAGACA TAATCAATTA ATAGGATGTA 5460

TTTGCTTAGA TTTGAGTAGG CATTTATGAC TGATGTTTTA AAATTTTTAT TTGATTTTAT 5520

35 GAAAATATAC CTGTTTGTAT TTGGTTTGGT TTGGTTTGAG TTTTGTATTTAT TTGAGACAGG 5580

GCTTCTCTGT GTAGTCCTGG CTGTCCTTGG AACTCACTCT GTAGACCAGG CTGGCCTTGA 5640

ACTCAGAAAT CCGCCTGCTT GTGCTTCCCA AGTGCTTAGA TTAAAGGTGT GCACTGCCAT 5700

TCAGCAAAAT TGCATACTTT AACCCAGTA TTTGGGAGGC AGAGGCAGAC TAATGTGTGA 5760

5 ATTCCAGGCT AGCCAAGGAT ACAGAGTGAG ACCCTATTCT TACCCTCCCC CCCCCAAACC 5820

CCAAAATGTA TTTTGTGCTT GTGTATGTAC ATGTGTGTTG CAGCACGTAA ATGTCCAAGG 5880

10 ACAACTTGTA GAAGTTCTCT CCGTTCACAG TCTAAGTCCT GAATTCAAAC TAAGGTCCTC 5940

AGGCTTAGCC ACAGTCTTCT TTATGTACTG AGCCATTTC A CTGGCCCTGG ATTGACTGAT 6000

GAATTAATTT TTGAGATAAG GTCTCTTGTA GCTCTAGCTA GGCTCAAAC ATGAACTCCC 6060

15 AAGGTCATCT TGAGCTGCTG GTACTCTTGC TTCCACCCCA AGTGGTGGA TGATACTCAG 6120

GCAGCACTTC TCTGGGGAAG GGGCTGGCCT TGGCCTTGAT TTTGTTGCCT CAGCTTCAAT 6180

GAGTGCTTGG GTCTCGTTGT TTCTTTTCTT TATCTGTGAA ATGGGTGAAC ACCTGTTCAA 6240

20 GACTTCCTGA CTCTTGAAAC ATCCAGGCAG GGTGAGGGAC TTGAAGTGGG CTCATCCCAT 6300

GCCTAACAAA GTGTCGTCTT TGACCCCA GACAGCTGTA ATCAGCCCCC AGGACCCAC 6360

25 CCTTCTCATC GGCTCCTCCC TGCAAGCTAC CTGCTCTATA CATGGAGACA CACCTGGGGC 6420

CACCGCTGAG GGGCTCTACT GGACCTTCAA TGGTCGCCGC CTGCCCTCTG AGCTGTCCCG 6480

CCTCCTTAAC ACCTCCACCC TGGCCCTGGC CCTGGCTAAC CTTAATGGGT CCAGGCAGCA 6540

30 GTCAGGAGAC AATCTGGTGT GTCACGCCCC AGACGGCAGC ATTCTGGCTG GCTCCTGCCT 6600

CTATGTTGGC TGTAAGTGGG GCCCCAGACA CTCAGAGATA GATGGGGGTT GGCAATGACA 6660

35 GATTTAGAGC CTGGGTCTTC TGTCCTGGGG CAGAGCCATG GGCTCTCACT TGCATGCAGG 6720

CATGGTCATA CCCAGCACAG GCATTGCAAC TCTAGGGACA GCTGTGGCTG CACTGTCCCC 6780

TGTGTACCCC ACAGCTTTAG AAAAGCTGTC ATGTTTTCTT TGTAGTGCCC CCTGAGAAGC 6840

CCTTTAACAT CAGCTGCTGG TCCCGGAACA TGAAGGATCT CACGTGCCGC TGGACACCGG 6900

5 GTGCACACGG GGAGACATTC TTACATACCA ACTACTCCCT CAAGTACAAG CTGAGGTTGG 6960

TACCCAGCCA AGCCTTGCTG TGTGACTTCT GGCAATACTT ACCTTCTCTG ATCAAATATG 7020

TTCCTGTTTA TGAACTCAAA AGGGACTCTC GCACCTCCAC AGGTGGTACG GTCAGGATAA 7080

10 CACATGTGAG GAGTACCACA CTGTGGGCCC TCACTCATGC CATATCCCCA AGGACCTGGC 7140

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15 TGATGTCCTC AACTGGATG TCCTGGACGT GGGTGAGCCC CCAGTGTCCA CCTGTGTTCT 7260

GCCCTAGACC TTATAGGGCG CCTCCCCCCC ATCCCCCAG ACTTTTGGT TCTTCTAGAG 7320

GTCTTAGCCA CAGCCACGGT GGTTGCAGGA CAGTGGTTGT TCATAACTTA ATGCAAAGAC 7380

20 TTTCCCCCAA GACAGTCAAG ATTTTCCCCT CCCCACCCCC AACACACACA TACACACACA 7440

CTCTGCAGAG AACACCTGGC CTGACCACCC TCCCTCTCTA CAGCCCAGGT GTTCAGAAGG 7500

25 GAGTCCTAGG GGAAGTGAAG GAGGCGCCCA GGTCTGAAGG CGCCCCAGGA AGCCGAGGCC 7560

TTGAGCTGGG GGGGGGGGCG AGGGTTGGAG GCACGAACTG GATGATCCCT GAGCACAAC 7620

GGGCCTAATC TAATTAGGGT GTTCCCAGCC CAAAGCAGCC TGGGCCATTT AACCCCTCAA 7680

30 GTGCCTCACT GAAGACTCAG GGGAGAGATC AGCTTGTAAT CTCTCCATGG TCCCCAGGA 7740

GGGTTCCTGG GTGCCCCCTG CTCATTCCCA CATCCAGAGG TTTTGTGTCT TCCTGGCATC 7800

35 TAACCCTCAG TTGTGCTCTG TGGCTGGCAC AGCTGCCCCG TGGAGGCTCT TGGTAATGTA 7860

CAAGGCATCA GAGGTGGACA TGGGATGGGG ATACATAGGG ATGGAGCCAA ATAGCACCTC 7920

AAGGTGGGGT GATATACAAT AAAGCTTGTC ACCCTGACGC TCAGAAAGCC TACTCATGAT 7980

GATCACAATT GTTGACATCA CTCTGGGACA TGTAGTGAGA CCCTAGCTCA AAACACAGAC 8040

5 AGTAGCTTTA AGAGTCAGCT TGTGACTTAA TACTGGAACT CAGGGCCTAA TAGGTGCTGG 8100

GTGATGCTCG CCTCACTCCC TGTTTAGTGA GATCTCTGCG CTAATCTCCA CCCCAGCTGG 8160

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10 TGGTAGCAGC AACTGCTGCT GGCTGTTTCT GGAATATTAA ATGACAGTAA TCTATCAGGC 8280

CTGGGTGAGT AGCTAACAGG GGTGGGGGCG TGGTCTGGAA AACGCAGATA GGGTCATAGG 8340

15 AGCCACTGCA GCCTAGATTA CACCACTGGG TGTTCTGTCA CTAGGCCATT CTCACCAAGC 8400

AGTCCTCAGA ACTGGGAGCA CTGTTGCCAG CATTTAATGC CAGCATTTAA TGCCAGCATT 8460

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20 AGCTCCAGGC CAGCCAGGGT GCGCAGTAAA ACCTTGCTC AAAAAACAAA GCATCTTTAG 8580

TGACCAGGCT TGCTCCACCC CCAGTGACCA CGGACCCCCC ACCCGACGTG CACGTGAGCC 8640

25 GCGTTGGGGG CCTGGAGGAC CAGCTGAGTG TGCGCTGGGT CTCACCACCA GCTCTCAAGG 8700

ATTTCTCTTT CCAAGCCAAG TACCAGATCC GCTACCGCGT GGAGGACAGC GTGGACTGGA 8760

AGGTGCCCCG CCCGCCCCGG ACCCGCCCCCT GACCCCGCCC CCCGCATCTG ACTCCTCCCT 8820

30 CACCGTGAG GTGGTGGATG ACGTCAGCAA CCAGACCTCC TGCGTCTCG CGGGCCTGAA 8880

GCCCGGCACC GTTTACTTCG TCCAAGTGCG TTGTAACCCA TTCGGGATCT ATGGGTGAG 8940

35 AAAGGCGGGA ATCTGGAGCG AGTGGAGCCA CCCCACCGCT GCCTCCACCC CTCGAAGTGG 9000

TGAGCACCTC TCCAGGGCTG GCTGGCCCAT GGAATCCCCA ATCCATCCTG TTCCTTCCCC 9060

CCCACCCTTT TTTTGAGACA GCGTCTTCAG GTAGCGCATG CTGGCCTTAA ATTCAGTATG 9120

TAGTCAAGGA TGACCTCGAG CTCCTGGTCT TTTTGTCTCC ACTTAGAGAC AATGGCCAGT 9180

5 GGCCATCACC ACCTTTGGGA GACTAGCCAT GGAGTCTATT TAGCCTGTCA TTTGGTGACA 9240

GATGGAGTAC AACAGTGTGA CCTCTTGTA GAGAACTGAA GACAGGCTGT TTTTAACCCC 9300

AATATCCTAG GCTCTCTAGA GGTAACTTT ATATAAAATA GAGACTATTA CAGCCAGTTA 9360

10 TCACATGGTC CCACAGAACC TTTTGTGACA CAACCTATAG ACCACAGTGC CTGTGCCTAC 9420

CACATAAGGG TCTCTACTGC TGGCCACCCC CTCCAACCCT TAAAAGGTAA CCTAGGCAGC 9480

15 CTTAATATTT GCAATCCTCC TACCTCAGCC TCTTGAATGC TCAGAAACCA GGCATTAACC 9540

CAAGTTTCTC TTCTCTGGGT CCCTTTCTTA AGGTGGGAGG GCCTAAAGAT GACTTCCTTT 9600

GTCCTGAAGA CTCTCCGAGC CCATGGATCT GCACTCTCTA ATATGAAATA TATTGCATAA 9660

20 AATGTCTGGC CTCAGTTTCC CCACCTGTCA GGTTTAGGCA GCACAGTCGG TCCAAGACAC 9720

TTCATTATTT GCAGGCAGTA TAAGAAGAAG CTCCCATCCC CCACCCGCTT CCTCCGGTCC 9780

25 CTAAGACAGA ATACTTCTAC ACTGAACTG AACTCTCGCA GACGCATATG CTCACTTTAA 9840

TGATGATGAA ATAATGGGGA AACTGAGGCT CCGAGAGATT CCTGGAGGAA GAGGGTCAAA 9900

ACCAGCTCCA GGAAGCTCTC CAGCCCCCAT CCGGGCCTCT CCAGGTTCTG GGCTTGGCGG 9960

30 GAGTGAACAC AGCTGGGAGG GGCTGGAGCC TGGGAGCTTT GGCCCTTGCT CGTGCCACAGC 10020

ACCTGCGATT CTTGCACGGG AGCCAGCAGG CGGCTGCGTC CGCCGAGAG ACTGAAGAAG 10080

35 CCGGGGGTAG GGTGGAGGG AGGTAAGCAG GGGCTGTGGG GGCCGAAGCT TGTGCCAGGG 10140

CCTGTCAGCG AGTCCCCAGT TTTATTTATG GCGTGAGGCC GATGTCCTTA TCCGCTGGCC 10200

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TGCTGGGGGA TGGCTGCGGC TGGGGATTGG ACCCAAGGGC TGGCTTCCCA CTCAGTCCTC 10260
CAGCCCCTC CATGTCACAC CCGTGCATTG TCTGAGGCTT ATCTTGGGAA CCCGCCCTTG 10320
TTCTGTGCTG TCTGTCTCTA TTTCTGTCAT TCACTTTCCC AGAGCCTTTT TTTTATGCTT 10380
TTAATATAAC TACGTTTAA AAATTGCTTT TGTATAATGT GTGTGCCTTC GTGAGCGTGC 10440
GTGCCACAAC ACACACGTGA AGGTTAGAGA ACTTTGTTGA GTAGGCTCCT TCCACCATGT 10500
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CTTCCCATCC TGTTTGGATA GTCATAGGTA ATCGAAGGTA AATCGCTGGC TTTAATTTTCG 10620
TAGCTATCCT GCCTCAGCCT ACCAAGTGCT GTGCTACCAC GTTTGTGGGA GGGGCTCTCC 10680
TCCCAGTGTC TGGGGGTACA CAGTCCCAAG ATCTCTGCTT TCTAGGTCTT TGTCTTAGTT 10740
TGCCCCCTTG TTTGTCCGTG TCCCTAGAGT CTCCGGCCCC ACTTAGTCTC CATTGATTTC 10800
CTTTCTGACC GAATACTCGG TTTTACCTCC CACTGATTG ACTCCCTCCT TTGCTTGTCT 10860
CCATCGCCGT GGCATTGCCA TTCCTCTGGG TGA CTCTGGG TCCACACCTG ACACCTTTCC 10920
CAACTTTCCC CAGCCGAAGC TGGTCTGGTA TGGGAGGCCG CCGTCCCGCG CGCGCCTCCT 10980
GCTGGCCGCG CCCCAACACT GCCGCTCCAT TCTCTTTAGA GCGCCCGGGC CCGGGCGGGC 11040
GGGTGTGCGA GCCGCGGGGC GGCGAGCCCA GCTCGGGCCC GGTGCGGCGC GAGCTCAAGC 11100
AGTTCCTCGG CTGGCTCAAG AAGCACGCAT ACTGCTCGAA CCTTAGTTTC CGCCTGTACG 11160
ACCAGTGGCG TGCTTGATG CAGAAGTCAC ACAAGACCCG AAACCAGGTA GGAAAGTTGG 11220
GGGAGGCTTG CGTGGGGGGT AAAGGAGCAG AGGAAGAGAG AGACCCGGGT GAGCAGCCTC 11280
CACAAACCCG CACTCTTCTT TCCAAGCACA GGACGAGGGG ATCCTGCCCT CGGGCAGACG 11340

GGGTGCGGCG AGAGGTAAGG GGGTCTGGGT GAGTGGGGCC TACAGCAGTC TAGATGAGGC 11400

CCTTTCCCCT CCTTCGGTGT TGCTCAAAGG GATCTCTTAG TGCTCATTTT ACCCACTGCA 11460

5 AAGAGCCCCA GGTTTTACTG CATCATCAAG TTGCTGAAGG GTCCAGGCTT AATGTGGCCT 11520

CTTTTCTGCC CTCAGGTCCT GCCGGCTAAA CTCTAAGGAT AGGCCATCCT CCTGCTGGGT 11580

CAGACCTGGA GGCTCACCTG AATTGGAGCC CCTCTGTACC ATCTGGGCAA CAAAGAAACC 11640

10 TACCAGAGGC TGGGCACAAT GAGCTCCAC AACCACAGCT TTGGTCCACA TGATGGTCAC 11700

ACTTGATAT ACCCCAGTGT GGGTAGGGTT GGGGTATTGC AGGGCCTCCC AAGAGTCTCT 11760

15 TTAAATAAAT AAAGGAGTTG TTCAGGTCCC GATGGCCAGT GTGTTTGGGG CCTATGTGCT 11820

GGGGTGGGGG GA 11832

20 (2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 26 amino acids
- (B) TYPE: amino acids
- 25 (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: Protein

30

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

35 Val Ile Ser Pro Gln Asp Pro Thr Leu Leu Ile Gly Ser Ser Leu Gln Ala Thr Cys Ser

5 10 15 20

Ile His Gly Asp Thr Pro

25

CLAIMS:

1. A nucleic acid molecule comprising a sequence of nucleotides encoding or complementary to a sequence encoding a novel haemopoietin receptor or derivative thereof having the motif:

Trp Ser Xaa Trp Ser [SEQ ID NO:1],

- 10 wherein Xaa is any amino acid.

2. A nucleic acid molecule according to claim 1 wherein Xaa is Asp or Glu.

- 15 3. A nucleic acid molecule according to claim 1 or 2 wherein said nucleic acid molecule is capable of hybridisation under low stringency conditions at 42°C to:

20 5N (A/G)CTCCA(A/G)TC(A/G)CTCCA 3N [SEQ ID NO:7]; and
5N (A/G)CTCCA(C/T)TC(A/G)CTCCA 3N [SEQ ID NO:8].

- 25 4. A nucleic acid molecule according to claim 3 comprising a sequence of nucleotides substantially as set forth in SEQ ID NO:12 or a nucleotide sequence having at least 60% similarity to the nucleotide sequence set forth in SEQ ID NO:12 or a nucleotide sequence capable of hybridising thereto under low stringency conditions at 42°C.

- 30 5. A nucleic acid molecule according to claim 3 comprising a sequence of nucleotides substantially as set forth in SEQ ID NO:14 or a nucleotide sequence having at least 60% similarity to the nucleotide sequence set forth in SEQ ID NO:14 or a nucleotide sequence capable of hybridising thereto under low stringency conditions at 42°C.

35

6. A nucleic acid molecule according to claim 3 comprising a sequence of nucleotides substantially as set forth in SEQ ID

NO:16 or a nucleotide sequence having at least 60% similarity to the nucleotide sequence set forth in SEQ ID NO:16 or a nucleotide sequence capable of hybridising thereto under low stringency conditions at 421C.

5

7. A nucleic acid molecule according to claim 3 comprising a sequence of nucleotides substantially as set forth in SEQ ID NO:18 or 24 or a nucleotide sequence having at least 60% similarity to the nucleotide sequence set forth in SEQ ID NO:18 or 24 or a nucleotide sequence capable of hybridising thereto under low stringency conditions at 421C.

10

8. A nucleic acid molecule according to claim 3 comprising a sequence of nucleotides substantially as set forth in SEQ ID NO:28 or a nucleotide sequence having at least 60% similarity to the nucleotide sequence set forth in SEQ ID NO:28 or a nucleotide sequence capable of hybridising thereto under low stringency conditions at 421C.

15

9. A nucleic acid molecule according to claim 3 comprising a sequence of nucleotides substantially as set forth in SEQ ID NO:38 or a nucleotide sequence having at least 60% similarity to the nucleotide sequence set forth in SEQ ID NO:38 or a nucleotide sequence capable of hybridising thereto under low stringency conditions at 421C.

20

25

10. A nucleic acid molecule according to claim 4 or 5 or 6 or 7 or 8 or 9 wherein said haemopoietin receptor is of murine origin.

30

11. A nucleic acid molecule according to claim 9 wherein said haemopoietin receptor is of human origin.

12. An expression vector comprising a nucleic acid molecule selected from the list consisting of:

35

- (i) a nucleotide sequence as set forth in SEQ ID NO:12;
- (ii) a nucleotide sequence as set forth in SEQ ID NO:14;

- (iii) a nucleotide sequence as set forth in SEQ ID NO:16;
- (iv) a nucleotide sequence as set forth in SEQ ID NO:18;
- (v) a nucleotide sequence as set forth in SEQ ID NO:24;
- (vi) a nucleotide sequence as set forth in SEQ ID NO:28; and
- 5 (vii) a nucleotide sequence as set forth in SEQ ID NO:38.

13. A method for cloning a nucleotide sequence encoding a haemopoietin receptor having the characteristics of NR6 or a derivative thereof, said method comprising searching a
10 nucleotide database for a sequence which encodes an amino acid sequence as set forth in one or more of SEQ ID NO:1, SEQ ID NO:7 and/or SEQ ID NO:8, designing one or more oligonucleotide primers based on the nucleotide sequence located in said search, screening a nucleic acid library with said one or more
15 oligonucleotides and obtaining a clone therefore which encodes NR6 or a part or derivative thereof.

14. An isolated nucleic acid molecule comprising a sequence of nucleotides encoding a haemopoietin receptor or derivative
20 thereof having an amino acid sequence substantially as set forth in SEQ ID NO:13 or having at least about 50% similarity thereto.

15. An isolated nucleic acid molecule comprising a sequence of nucleotides encoding a haemopoietin receptor or derivative
25 thereof having an amino acid sequence substantially as set forth in SEQ ID NO:15 or having at least about 50% similarity thereto.

30 16. An isolated nucleic acid molecule comprising a sequence of nucleotides encoding a haemopoietin receptor or derivative thereof having an amino acid sequence substantially as set forth in SEQ ID NO:17 or having at least about 50% similarity thereto.

35

17. An isolated nucleic acid molecule comprising a sequence of nucleotides encoding a haemopoietin receptor or derivative

thereof having an amino acid sequence substantially as set forth in SEQ ID NO:19 or having at least about 50% similarity thereto.

5 18. An isolated nucleic acid molecule comprising a sequence of nucleotides encoding a haemopoietin receptor or derivative thereof having an amino acid sequence substantially as set forth in SEQ ID NO:25 or having at least about 50% similarity thereto.

10 19. An isolated nucleic acid molecule comprising a sequence of nucleotides encoding a haemopoietin receptor or derivative thereof having an amino acid sequence substantially as set forth in SEQ ID NO:29 or having at least about 50% similarity thereto.

15 20. An isolated novel haemopoietin receptor comprising the amino acid motif:

20 Trp Ser Xaa Trp Ser [SEQ ID NO:1]

wherein Xaa is any amino acid.

25 21. An isolated haemopoietin receptor according to claim 20 wherein Xaa is Asp or Glu.

30 22. An isolated haemopoietin receptor according to claim 21 comprising the amino acid sequence substantially as set forth in SEQ ID NO:13.

23. An isolated haemopoietin receptor according to claim 21 comprising the amino acid sequence substantially as set forth in SEQ ID NO:15.

35 24. An isolated haemopoietin receptor according to claim 21 comprising the amino acid sequence substantially as set forth in SEQ ID NO:17.

25. An isolated haemopoietin receptor according to claim 21 comprising the amino acid sequence substantially as set forth in SEQ ID NO:19.

5 26. An isolated haemopoietin receptor according to claim 21 comprising the amino acid sequence substantially as set forth in SEQ ID NO:25.

10 27. An isolated haemopoietin receptor according to claim 21 comprising the amino acid sequence substantially as set forth in SEQ ID NO:29.

15 28. A method for modulating expression of NR6 in a mammal, said method comprising contacting a genetic sequence encoding said NR6 with an effective amount of a modulator of NR6 expression for a time and under conditions sufficient to up-regulate or down-regulate or otherwise modulate expression of NR6, wherein the genetic sequence encoding said NR6 is selected from the nucleotide sequence set forth in SEQ ID NO:12 or 14 or 20 16 or 18 or 24 or 28 or 38 or is a sequence having at least about 60% similarity to at least one of SEQ ID NO:12 or 14 or 16 or 18 or 24 or 28 or 38 and is capable of hybridising thereto under low stringency conditions at 42°C.

25 29. A method of modulating activity of NR6 in a mammal, said method comprising administering to said mammal, a modulating effective amount of a molecule for a time and under conditions sufficient to increase or decrease NR6 activity wherein said NR6 comprises an amino acid sequence:

30 (i) encoded by a nucleotide sequence selected from the nucleotide sequence set forth in SEQ ID NO:12 or 14 or 16 or 18 or 24 or 28 or 38 or a nucleotide sequence having at least 60% similarity to the nucleotide sequence set forth in SEQ ID NO:12 or 14 or 16 or 18 or 24 or 28 or 38 35 and which is capable of hybridising thereto under low stringency conditions at 42°C; and

(ii) substantially as set forth in SEQ ID NO:12 or 14 or 16 or 18 or 32 or 30 or a sequence having at least 50% similarity thereto.

5 30. A pharmaceutical composition comprising an NR6 receptor in soluble form and one or more pharmaceutically acceptable carriers and/or diluents wherein said NR6 comprises the amino acid sequence:

- 10 (i) encoded by a nucleotide sequence selected from the nucleotide sequence set forth in SEQ ID NO:12 or 14 or 16 or 18 or 24 or 28 or 38 or a nucleotide sequence having at least 60% similarity to the nucleotide sequence set forth in SEQ ID NO:12 or 14 or 16 or 18 or 24 or 28 or 38
15 and which is capable of hybridising thereto under low stringency conditions at 42°C; and
(ii) substantially as set forth in SEQ ID NO:12 or 14 or 16 or 18 or 32 or 30 or a sequence having at least 50% similarity thereto.

20

31. An isolated antibody or a preparation of antibodies to an NR6 receptor, said NR6 receptor comprising the amino acid sequence:

- 25 (i) encoded by a nucleotide sequence selected from the nucleotide sequence set forth in SEQ ID NO:12 or 14 or 16 or 18 or 24 or 28 or 38 or a nucleotide sequence having at least 60% similarity to the nucleotide sequence set forth in SEQ ID NO:12 or 14 or 16 or 18 or 24 or 28 or 38
30 and which is capable of hybridising thereto under low stringency conditions at 42°C; and
(ii) substantially as set forth in SEQ ID NO:12 or 14 or 16 or 18 or 24 or 28 or 38 or a sequence having at least 50% similarity thereto.

35

32. A transgenic animal comprising a mutation in at least one allele of the gene encoding NR6.

33. A transgenic animal according to claim 33 comprising a mutation in two alleles of the gene encoding NR6.

34. A transgenic animal according to claim 33 or 34 wherein
5 said animal is a murine animal.

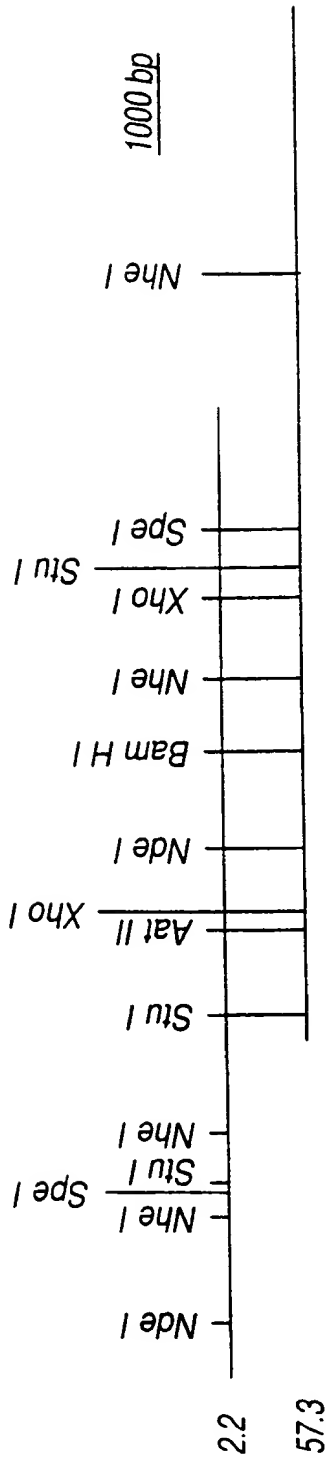


Fig. 1A

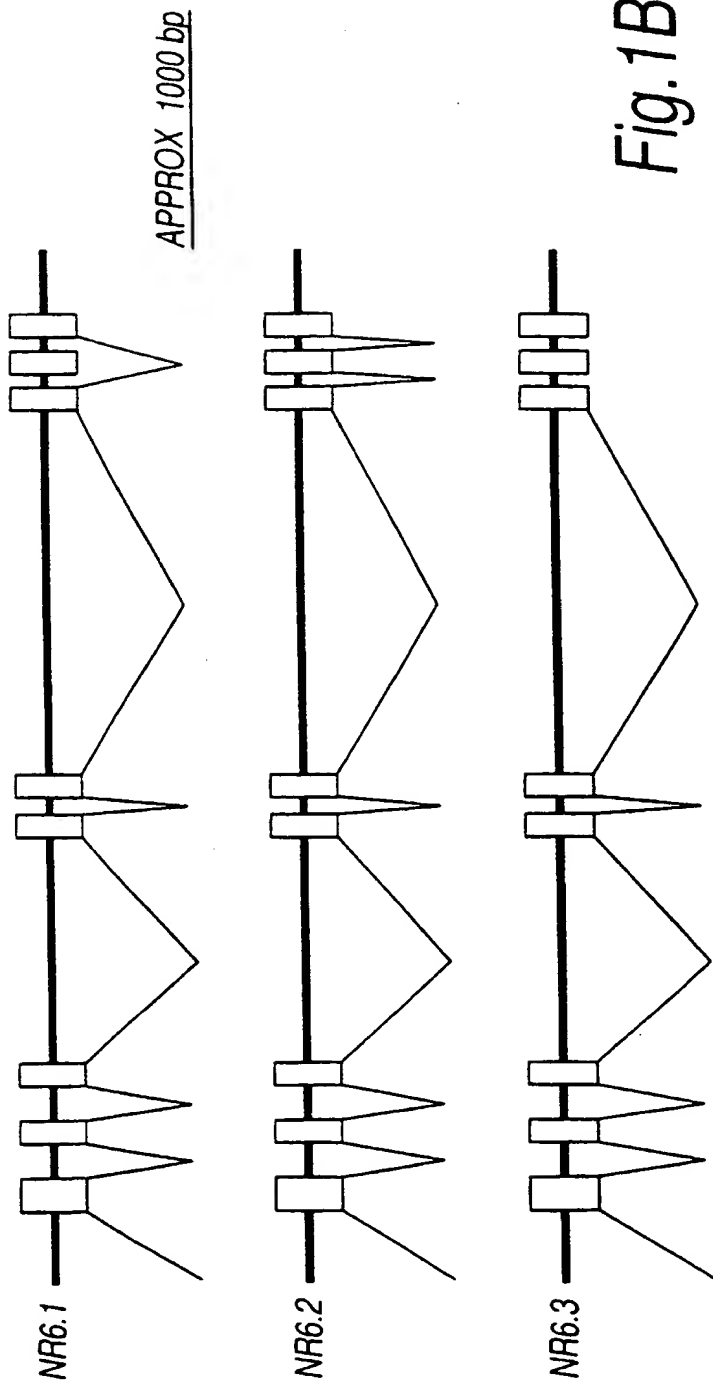


Fig. 1B

$2/43$

$3/43$	$4/43$
$5/43$	$6/43$
$7/43$	$8/43$
$9/43$	$10/43$
$11/43$	$12/43$
$13/43$	$14/43$
$15/43$	$16/43$
$17/43$	$18/43$

Fig.2

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g1	cccagaactct
g38	agtttcaagacagtgtgtt
g83	aagaaaagaaataaagaga
g128	cagcttgggtgggtaagggg
g173	agcccccattccctaggaatc
g218	cagctgctgacctccatac
g263	ggagacataatcaattaat
g308	ggcattttatgactgatgtt
g353	aatataacctgtttgtattt
g398	atttgagacagggcttctc
g443	tcactctgtagaccaggct
g488	ttgtgcttcccaagtgtt
g533	gcaaaattgcataactttaa
g578	actaatgtgtgaattccag
g623	ctattcttaccctcccccc
g668	ttgtgtatgtacatgtgtg
g713	acttgtagaagttctctcc
g758	actaaggctcctcaggctta
g803	catttcactggccctggat
g848	aggctctcttgtagctctag
g893	gtcatcttgagctgctggg
g938	aatgatactcaggcagcac
g983	ccttgattttgttgacctca
g1028	gtttctttttctttatctgt
g1073	ttcctgactcttgaaacat

Fig.2(i)

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tggacgctgagggcaggaggattccca
tctaggtaatgagaccctgtcaagaa
caagaaaatgtttatataggctgtgaga
cacttgcctccaatcaagatgacctc
catggtagaaggagaaagcaaactcg
atgtgctccaatgtgcacacacacag
aggatgtattttgcttagattttgagta
ttaaaattttttattttgatttttatgaa
ggttttggttttggttttgagttttgttt
tgtgtagtcctggctgtccttgggaac
ggccttgaactcagaaatccgcctgc
agattaaagggtgtgcactgccattca
ccccagtattttgggagggcagaggcag
gctagccaaggatacagagtgagacc
ccaaaacccccaaaatgtatttttgtgc
ttgcagcacgtaaatgtccaaggaca
gttcacagtctaagtcctgaattcaa
gccacagtcttcttttatgtactgagc
tgactgatgaattaatttttgagata
ctaggctcaaactatgaactcccaag
actcttgcttccaccccaagtgggtgg
ttctctgggggaaggggctggccttgg
gcttcaatgagtgcttgggtctcgtt
gaaatgggtgaacacctgttcaagac
ccagggcagggtgagggacttgaagtg

Fig.2(ii)

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g1118	ggctcatcccatgcctaac
g1163	agctgtaatcagccccccag
g1208	<u>L Q A T C S</u> <u>CCTGCAAGCTACCTGCTCT</u>
g1253	<u>A E G L Y W</u> <u>CGCTGAGGGGCTCTACTGG</u>
g1298	<u>E L S R L L</u> <u>TGAGCTGTCCCGCCTCCTT</u>
g1343	<u>A N L N G S</u> <u>GGCTAACCTTAATGGGTCC</u>
g1388	<u>C H A R D G</u> <u>GTGTCACGCCCGAGACGGC</u>
g1433	<u>V G</u> <u>TGTTGGCT</u> gtaagtgggggc
g1478	ttggcaatgacagatttag
g1523	agccatgggctctcacttg
g1568	aggcattgcaactctaggg
g1613	gtaccccacagctttagaa

Fig.2(iii)

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aaagtgtcgtcctttgaccccagacac
D P T L L I G S S
GACCCACCCCTTCTCATCGGCTCCTC

I H G D T P G A T
ATACATGGAGACACACCTGGGGCCAC

T F N G R R L P S
ACCTTCAATGGTCGCCGCCTGCCCTC

N T S T L A L A L
AACACCTCCACCCTGGCCCTGGCCCT

R Q Q S G D N L V
AGGCAGCAGTCAGGAGACAATCTGGT

S I L A G S C L Y
AGCATTCTGGCTGGCTCCTGCCTCTA

cccagacactcagagatagatggggg

agcctgggtccttctgtcctgggggcag
catgcaggcatgggtcatacccgagcac
acagctgtggctgcactgtcccctgt

L
aagctgtcatgttttccttgtagTGC

Fig.2(iv)

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g1658	P P E K P F N <u>CCCCTGAGAAGCCCTTTAA</u>
g1703	K D L T C R W <u>AGGATCTCACGTGCCGCTG</u>
g1748	F L H T N Y S <u>TCTTACATACCAACTACTC</u>
g1793	ccagccaagccttgctgtg
g1838	tgatcaaatatgttcctgt
g1883	W Y G cctccacag <u>GTGGTACGGT</u>
g1928	T V G P H S <u>CACTGTGGGCCCTCACTCA</u>
g1973	F T P Y E I <u>CTTCACTCCCTATGAGATC</u>
g2018	S A R S D V <u>CTCAGCAAGATCTGATGTC</u>
g2063	tgagccccccagtgtccacc
g2108	cgcctcccccccatcccc
g2153	ttagccacagccacggtgg
g2198	taatgcaaagactttcccc

Fig.2(v)

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I	S	C	W	S	R	N	M
<u>CATCAGCTGCTGGTCCCGGAACATGA</u>							
T	P	G	A	H	G	E	T
<u>GACACCGGGTGCACACGGGGAGACAT</u>							
L	K	Y	K	L	R		
<u>CCTCAAGTACAAGCTGAG</u> gttggtac							
tgacttctggcaatacttaccttctc							
ttatgaactcaaaagggactctcgca							
Q	D	N	T	C	E	E	Y H
<u>CAGGATAACACATGTGAGGAGTACCA</u>							
C	H	I	P	K	D	L	A L
<u>TGCCATATCCCCAAGGACCTGGCCCT</u>							
W	V	E	A	T	N	R	L G
<u>TGGGTGGAAGCCACCAATCGCCTAGG</u>							
L	T	L	D	V	L	D	V
<u>CTCACACTGGATGTCCTGGACGTGG</u> g							
tgtgttctgccctagaccttataggg							
cagactttttgggttcttctagaggtc							
ttgcaggacagtgggttggttcataact							
caagacagtcaagatttttcccctcc							

Fig.2(vi)

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g2243	ccaccccccaacacacacat
g2288	ggcctgaccaccctccctc
g2333	gtcctaggggactgagagg
g2378	ggaagccgaggccttgagc
g2423	acgaactggatgatccctg
g2468	ggtgttcccagcccaaagc
g2513	gcctcactgaagactcagg
g2558	tgggtccccccaggagggttc
g2603	tccagagggttttgtgtctt
g2648	ctgtggctggcacagctgc
g2693	aggcatcagagggtggacat
g2738	caaatagcacctcaagggtg
g2783	cctgacgctcagaaagcct
g2828	tcactctgggacatgtagt
g2873	tagctttaagagtcagctt
g2918	taatagggtgctgggtgatg
g2963	tctctgcgctaatactccac
g3008	cttgaggggcaggaaatgtgt
g3053	gtagcagcaactgctgctg
g3098	taatctatcaggcctgggt
g3143	gtctggaaaacgcagatag
g3188	ttacaccactgggtgttct
g3233	tcctcagaactgggagcac
g3278	taatgccagcattagggga
g3323	ttcaaggccatcctgaatt
g3368	ggtgcgagtaaaaccttg

Fig.2(vii)

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acacacacactctgcagagaacacct
tctacagcccagggtgttcagaaggga
aggcgcccagggtctgaaggcgcccca
tggggggggggggggcgagggttggaggc
agcacaactggggcctaataattag
agcctggggccattttaacccttcaagt
ggagagatcagcttgtactctctcca
ctgggtgccccctggctcattcccaca
cctggcatctaaccctcagttgtgct
cccgtggagggtcttggtaatgtaca
gggatggggatacatagggatggagc
gggtgatatacaataaagcttgtcac
actcatgatgatcacaattgttgaca
gagaccctagctcaaaacacagacag
gtgacttaataactggaactcagggcc
ctcgccctcactccctgttttagtgaga
cccagctgggtggggctgctctgtccc
gtcttccatcagagataggaccctgtg
gctgtttctggaatatataatgacag
gagtagctaacaggggtggggggcggtg
ggtcataggagccactgcagcctaga
gtcactaggccatttctcaccaagcag
tgttgccagcatttaatgccagcatt
ggcagaggcagaaggatctctctgag
tacataaagagctccaggccagccag
tctcaaaaaacaaagcatcttttagtg

Fig.2(viii)

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g3413	accaggcttgctccacccc
g3458	V H V S R V G GTGCACGTGAGCCGCGTTG
g3503	R W V S P P CGCTGGGTCTCACCACCAG
g3548	K Y Q I R Y <u>AAGTACCAGATCCGCTACC</u>
g3593	gtgcccgtcccgcgcccgga
g3638	ctgactcctccctcaccgt
g3683	Q T S C R L A <u>AGACCTCCTGCCGTCTCGC</u>
g3728	F V Q V R C N <u>TCGTCCAAGTGCGTTGTAA</u>
g3773	K A G I W S E <u>AGGCGGGAATCTGGAGCGA</u>
g3818	T P R S <u>CCCCTCGAAGTG</u> gtgagca
g3863	aatccccaatccatcctgt

Fig.2(ix)

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V T T D P P P D
cagTGACCACGGACCCCCCACC CGAC

G L E D Q L S V
GGGGCCTGGAGGACCAGCTGAGTGTg

A L K D F L F Q A
CTCTCAAGGATTTCCTCTTCCAAGCC

R V E D S V D W K
GCGTGGAGGACAGCGTGGACTGGAAG
cccgccccctgacccccgcccccccgcat

V V D D V S N
gcagGTGGTGGATGACGTCAGCAACC

G L K P G T V Y
GGGCCTGAAGCCCGGCACCGTTTACT

P F G I Y G S K
CCCATTCGGGATCTATGGGTCGAAAA

W S H P T A A S
GTGGAGCCACCCCACCGCTGCCTCCA

cctctccagggtggctggcccatgg
tccttccccccccaccctttttttgag

Fig.2(x)

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g3908	acagcgtcttcaggtagcg
g3953	gtcaaggatgacctcgagc
g3998	gacaatggccagtggccat
g4043	agtctattttagcctgtcat
g4088	tgacctcttgtaagagaac
g4133	tatcctagggtctcttagag
g4178	ttacagccagttatcacat
g4223	acctatagaccacagtgcc
g4268	tgctggcccacccctccaa
g4313	taatatttgcaatcctcct
g4358	ccaggcattaacccaagtt
g4403	gtgggaggggcctaaagatg
g4448	agcccatggatctgcactc
g4493	tgtctggcctcagtttccc
g4538	cggtccaagacacttcatt
g4583	cccatccccccacccgcttc
g4628	tacactgaaactgaactct
g4673	atgatgaaataatgggggaa
g4718	gaagagggtcaaaaccagc
g4763	gggcctctccagggttctgg
g4808	aggggctggagcctgggag
g4853	ctgcgattcttgcacggga
g4898	gagactgaagaagccgggg
g4943	gctgtggggggccgaagctt
g4988	agttttatttatggcggtga
g5033	ctggggggatggctgcggct

Fig.2(xi)

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catgctggccttaaatttcagtatgta
tcctgggtcctttttgtctccacttaga
caccacctttgggagactagccatgg
ttgggtgacagatggagtacaacagtg
tgaagacaggctgttttttaaccccaa
gttaactttatataaaaatagagacta
gggtcccacagaacctttttgtcacaca
tgtgcctaccacataagggtctctac
cccttaaaaggtaacctaggcagcct
acctcagcctcttgaatgctcagaaa
tctcttctctgggtccctttcttaag
acttcctttgtcctgaagactctccg
tctaatatgaaatatattgcataaaa
cacctgtcagggtttaggcagcacagt
atttgcaggcaggtataagaagaagct
ctccgggtccctaagacagaatacttc
cgcagacgcatatgctcactttaatg
actgagggtccgagagattcctggag
tccaggaagctctccagcccccatcc
gcttggcgaggagtgaacacagctggg
ctttggcccttgctcgtgccccagcac
gccagcaggcggctgcgtccgcccga
gtagggttggaggaggtaagcaggg
gtgccaggggcctgtcagcgagtcccc
ggccgatgtccttatccgctggcctg
ggggattggaccaagggtggttc

Fig.2(xii)

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g5078	ccactcagtcctccagccc
g5123	tgaggcttatcttgggaac
g5168	ctatttctgtcattcactt
g5213	aatataactacgtttttaa
g5258	ttcgtgagcgtgcgtagcca
g5303	tttggttagtaggctcctt
g5348	caagagcaattactgagtc
g5393	tcccatcctgtttggatag
g5438	ggctttaatttcgtagcta
g5483	gctaccacgtttgtgggag
g5528	gacacagtcaccaagatctc
g5573	gcccccttgcttttgctccgtgt
g5618	cattgactgggtctttcctt
g5663	ctgatttgactccctcctt
g5708	ccattcctctgggtgactc
g5753	actttccccagccgaagct
g5798	gcgcgcgcctcctgctggc

	E R P G
g5843	tcttttag <u>AGCGCCCGGGCC</u>

	G G E P S S
g5888	<u>GGCGGCGAGCCCAGCTCGG</u>

	F L G W L K
g5933	<u>TTCCTCGGCTGGCTCAAGA</u>

	F R L Y D Q
g5978	<u>TTCCGCCTGTACGACCAGT</u>

Fig.2(xiii)

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actccatgtcacacccgtgcattctc
ccgcccttggttctgtgctgtctgtct
tcccagagccttttttttatgctttt
aattgctttttgtataatgtgtgtgcc
caacacacacgtgaagggttagagaac
ccaccatgtgggactagggctggcga
atctcgccagcccctcacccctcact
tcataggtaatcgaaggtaaatacgct
tcctgcctcagcctaccaagtgtgtgt
gggctctcctcccagtggtctgggggt
tgcttttctagggtctttgtcttagttt
ccctagagtgctccggccccacttatc
taccgaatactcggttttacctccca
tgcttggtctccatcgccgtggcattg
tgggtccacacctgacacctttccca
ggctctgggtatgggaggccgccgtccc
cgcgccccaacactgccgctccattc

P G G G V C E P R
CGGGCGGCGGGGTGTGCGAGCCGCGG

G P V R R E L K Q
GCCCGGTGCGGCGCGAGCTCAAGCAG
K H A Y C S N L S
AGCACGCATACTGCTCGAACCTTAGT

W R A W M Q K S H
GGCGTGCTTGGATGCAGAAGTCACAC

Fig.2(xiv)

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g6023	K T R N Q V AAGACCCGAAACCAGGTAG
g6068	G K G A E E GGTAAAGGAGCAGAGGAAG
g6113	Q H R T L L CAACACCGCACTCTTCTTT
g6158	P R A D G V P S G R R G A CCTCGGGCAGACGGGGGTGC
g6203	GTGGGGCCTACAGCAGTCT
g6248	TGTTGCTCAAAGGGATCTC
g6293	GAGCCCCAGGTTTTACTGC
g6338	CTTAATGTGGCCTCTTTTC
g6383	* CTAAGGATAGGCCATCCTC
g6428	CTGAATTGGAGCCCCCTCTG
g6473	CCAGAGGCTGGGCACAATG
g6518	ACATGATGGTCACACTTGG
g6563	GGTATTGCAGGGCCTCCCA
g6608	TTGTTTCAGGTccccgatggc
g6653	ggtgggggga

Fig.2(xv)

18/43

G K L G E A C V G
GAAAGTTGGGGGAGGCTTGCGTGGGG

E R D P G E Q P P
AGAGAGACCCGGGTGAGCAGCCTCCA

S K H R T R G S C
D E G I L
CCAAGCACAGGACGAGGGGATCCTGC

R R E V R G S G *
A R

GGCGAGAGGTAAGGGGGTCTGGGTGA
AGATGAGGCCCTTTCCCCTCCTTCGG
TTAGTGCTCATTTCACCCACTGCAAA
ATCATCAAGTTGCTGAAGGGTCCAGG

V L P A K L
G P A G *
TGCCCTCAGGTCCTGCCGGCTAAACT

CTGCTGGGTCAGACCTGGAGGCTCAC

TACCATCTGGGCAACAAAGAAACCTA
AGCTCCCACAACCACAGCTTTGGTCC
ATATACCCCAGTGTGGGTAGGGTTGG
AGAGTCTCTTTAAATAAATAAAGGAG
cagtgtgtttggggcctatgtgctgg

Fig.2(xvi)

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20/43	21/43
22/43	23/43
24/43	25/43
26/43	27/43
28/43	29/43
30/43	31/43
32/43	33/43
34/43	35/43
36/43	37/43
38/43	39/43
40/43	41/43

Fig.3

20/43

GCGGCCGCTG	CAGTGATTAC	TCACCGCGTG
TTTTTCCGTG	GGGGGATGTG	AAGAAGTTTA
GGAATGCAGG	GTTTCGGTCCC	GTTCCCCAAA
AAGGGCTCCC	TGCACGCGCT	CCGGGACATC
TGAGAAGGGA	CCAGAGGCCG	GAGACTCCCT
ACGAAACGAG	ACTACAGCGA	TGGGAGAGGT
GACCCATGCA	CCCAGAGAAA	GGGACTGGTG
AGGGCTGAAA	GAGGATGAAC	GGGCTCAGGT
TGGGTATGGG	GGCCCCGTAA	GAGGGGCGGG
GGAGGGGATC	CTGGAAAAGC	ACCAGGGCTG
ACAGGATCCC	AGATGAGGGG	GTGGGAAGCC
CACGGGCTGG	TGGGGAAAGA	GTGGGGGGCT
GTA ACTGGGC	GGAGGCCGGC	CGGGCGGGGC
GTGCGGGGCC	CACGATCAAC	CCCCCCCCAG
CGGGGCGAGC	GGCGCATTAG	CGCCTTGTCA
CGCTGTCCGC	GCCCAGTGAC	GCGCGTGAGG
CGCCCCCGCC	CCATACCGGC	GTTGCAGTCA
GGGTCGCCCCG	GGCCCCGTCTG	CCCAATCCGC

Fig.3(i)

SUBSTITUTE SHEET (RULE 26)

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GCGCACCCCA	CCCGCGGGCC	GCTGAGTGGA	60
GGGAGAACTC	TTCTGCACCG	ATGGGAACTA	120
GGACACACCT	CTCCCCATAA	GCCCACTCAT	180
CCCATATCCA	ATACCCGCAG	ATATGATAGT	240
CCCTGCCTTC	TGGCTTTCCC	CCCCCCTGC	300
GGCATGAAGG	CTTAGGGTGG	GGATCGGTAG	360
GCAACTTTCA	AACTCTCTGG	GGAAGGAAGA	420
ACTGCTCAAT	GTGTGTGTGG	CGGACCAAAG	480
GAAGGTGGAT	AGGAAGGATC	CCGGTAGACT	540
CGAGCTAGGA	ACCCATTCGG	AGTTAAGGGT	600
TGGGACGGGC	GGGACCAGAG	AGGGAGGTCC	660
TCGCGCAGGA	GGATGGGACG	TTCAGGAGTG	720
GCGCGGTGCC	CGCGGGCGGT	GGGAAGGCCG	780
GGGCCGGGCC	GGGCCGGGGG	CGGGGCCGGG	840
ATTTTCGGCTG	CTCAGACTTG	CTCCGGCCTT	900
ACCCGAGCCC	CAATCTGCAC	CCCGCAGACT	960
CCGCCCGTTG	CGCGCCACCC	CCATGCCCGC	1020
GCGGCGGCCG	CCGCGGCCGC	TGTCCTCGCT	1080

Fig.3(ii)

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GTGGTCGCCT	CTGTTGCTCT	GTGTCCTCGG
GTACCGTGCG	CCCTGCTCCC	CACCTCCCCA
AGTCGCGGGG	GATGGAAGAA	GGGGCGCGAG
GGCGGCCCTC	GGGGCGCCCT	CACCTGTGGG
AGTACCCCGT	TATACATCAG	AGGCCTCTTA
AGGCTCAGTT	TGAAGGACAT	CGCAGTGTCC
GCTTCGGGGC	GCACGCCTGT	GTCTTGGATA
GGGCGCACGC	TTGGGTGCGT	TGGGTTGGGT
GAAGTGATGA	TCCCCGGGGG	GAGGGTGGGG
ATGCGGCCCG	GCGTCCCTCG	GGACTTGCCT
CTATAGCAGA	CTCCATGCTT	TGGTATCCTC
CGGTCTCATT	CAGGCTGCGC	TGGGTTGAGA
CGAGAGCAAG	CGTGTCCGGG	CACCGCGAGC
GGGGGTCAGC	TGCCGAGAGA	ATCCCAGTGT
ATCACCCAAC	GCACACATCC	CCGCCAGGAT
CACACCCAAA	GACACACAAA	AGAGCCCCAC
CGCGCGCTGC	AGCCCAGATG	CGTATTCGCA
ACACACACAC	ACACACACAC	ACACACACAC

Fig.3(iii)

SUBSTITUTE SHEET (RULE 26)

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GGTGCCTCGG	GGCGGATCGG	GAGCCCCGTGA	1140
GGGAAGCCGG	GATCCGGCGC	CCCGGGGGGT	1200
CGCCACCTGG	ACGTCCCGGG	AACAAAGGAA	1260
GCTCATGGCA	CCACCACCCA	GCCTCCCAAG	1320
TCTGTATCCC	CTTTGCGAGG	CTGTCTGGCC	1380
TGGGACCCCC	CTCCTTCAGG	GTGCTGGGAC	1440
TCAGAGCGGA	AGGGAAGCCT	CCCTGGCCGG	1500
GCTGGCGCAA	AGTGGGGTCC	CCTCCCCCAT	1560
CGTTATCGTG	AGCCCTCCTG	TCCGCCTGGC	1620
CTCCGTGGGG	TCGGCGCCGC	CCCCTCCCCC	1680
GAAGTCCTCT	CCACTGGTGG	GGCTCACAAC	1740
GCCTCTAGCG	ACTGAAATTT	CGGTGAGGAG	1800
CCAGACTTCA	TTGTCTAAGG	GGCACCCAGT	1860
CCCAGGAGGA	ACTCCTGGCC	TTGAGCCCCC	1920
GCGGTCTCCA	CATCCAGACC	CTCTCTGGGA	1980
TGGCTTATGT	CCCGTCACCC	TGCCCTCCGA	2040
CACCATCGCG	GCGCTCGCAT	TCCATCCTCT	2100
ACACACACAC	ACACACAGAC	ACGCACACAC	2160

Fig.3(iv)

SUBSTITUTE SHEET (RULE 26)

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ACACGCACGC	ACACACACGC	ACGCCCCGCAC
GCAACACCGG	GGTACGCATA	TGGTTGAGTG
ACCCCATCCG	GAGACACAGG	CCACACCGCA
TAGTAGTCTT	GTGCAGTTTG	TCCGCGGTGT
ACAGGAACCT	ACACTCCTGC	TTGCCCAAGG
GACCTTTCCG	GGGAGTTGGT	GTTGCTGCCA
GCGCTAAGCT	TTGTTTCCGG	GCGGGCTGCA
TGGCGCGTGT	GTTTTTTCTT	TTAAGGGGGA
TGCAATCTGT	TTGTACTTAC	CGTGTGTCTT
AAAGTGTATG	CAGGTACCAG	CGGGACAGGA
GAGGCCACCT	TCCCGTTGGC	CTTTCAGGGA
GTGTTCTTTT	TAATAACGGC	AGCAACTCCG
GGCCCCGGCT	TTGTGGAAAG	GAGGGGAAGA
GGCTTAGGGG	GCTGTCAGCT	GCTGCTCTGT
AGTGGCTTTG	GCCCATTGTT	TGTGGAAGCC
TACTCCAGAG	TCAGGCTTCT	CAGTCCGAGC
GAATCAGGGA	AGGGGGTGCC	AGGTGGACTA
AAGGAGAAAG	CTTGGGCTTG	CCCCCTCCC

Fig.3(v)

SUBSTITUTE SHEET (RULE 26)

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TCGTGGTCCC	ACATTTATTT	CACAGGGGAG	2220
CACTGGAGAT	CTTTCCCCAC	CACTCTCAGG	2280
GGGGCACCAC	GCTGCGCTGC	TGCTCTGGGC	2340
CTGTGGACGC	CCTCCCGCTC	TTGTCAGGGG	2400
CGGCTGGGCA	GGTGATGTGG	TGACACCCGG	2460
AGCCTGGGTA	GTTTTTGAAT	GCCACCAATA	2520
GAGCAACAGG	CGAAGGTGGC	GGAGTGGGGG	2580
GAGAAATTAA	ATAAGAGGTT	CTCACACCTC	2640
AACACCTGAC	CAGCCAGCCG	GTGGGTCGTA	2700
GATGGGGGCC	CCTGGGGTAT	GGCTGGGATG	2760
ATCTCACACT	TTTCCCTTTT	AAAACACATG	2820
CATTGGGAAA	GGGGGAAATA	AGCTTGTATA	2880
GGGAAGAAAA	AAGGAGGGGT	GTCTCCTCCA	2940
CTAGCTTGGC	ATGTGTGTGC	CCCAGTCCCC	3000
AAGAGGGAGA	CTGGAGTCCT	CTATCTCTGG	3060
CCAGAGAACG	TCTTCCCTGT	TTTATGGAGG	3120
CGTTCTGCTG	AGGACTGTAC	CAGTCGCTCG	3180
CCCTCAAGCC	ACGAAGGGCA	GCTGCTAGGC	3240

Fig.3(vi)

SUBSTITUTE SHEET (RULE 26)

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TAGTGTGGTA	AAAGGGCATT	ACTCCCCAGC
CAGACAAATG	CTGGGGGAGGG	ACAGAGGGGT
GGTCCCCGGGT	CGGGCAGTGC	CTCCCACCCT
GGGTGGGCCG	GGGTAGAGAC	GCTGGCACGT
GCGGGCGGCT	GGCTGCCTGG	GACCTCCGGG
GCCTGCTCCT	CCTGCTCCTT	CGCACGGACG
CCCAAATGCA	ACTGCGATTG	CAGGCTTCGC
CCTGGGAGAA	GTCATTCAGG	GCCCAGACTA
GGGCATGAAG	GACCGTCCAG	GGCTGCAGTT
GCAGCCTCTG	TTCTCCGAGC	CTCTTTGGAA
AATACTCTTT	TCCTCTCATC	CCATCCCCGGG
TGCAGTCTTC	CCTAACCTTT	TCTTTGCTTC
CCTCTCCCCT	TGCCCAACTG	GGGCTCCAGC
CAGGGCCTCT	CTGACACACA	GGGTTGTAGC
CTCTTTTGCT	TCTGAGACTT	AATTTTTTTC
TCTCTGTACA	GCCCTGGCTG	CCCTGGCACT
ACAAACCTAC	CTGCCTCTGC	CTTTCCAGTG
AGTAGTTAAG	TGTTTTGCTG	TGTCTTTATT

Fig.3(vii)

SUBSTITUTE SHEET (RULE 26)

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CAGGACCCCC	CAGAGAGTCC	CCTTCCTGGC	3300
GTGATCATTG	CCCAGGAGTG	CAGACAGTGG	3360
GCTGAGGGGG	GCGCCCAGGC	AGGAAGCGGT	3420
CCCAGTTCAT	GCCGAAGGAA	TTCTGAATTA	3480
GCGGCCCCCT	GGCCCCCGCC	GCTCCGTCTG	3540
CTGAGACCTC	CGCTGAGCCC	TGGGACAAGC	3600
AAGACCCGCC	TCCTCCCAAG	GCCAAATTTG	3660
GAACCATGTT	GGTGCCACCT	CATCCATCTG	3720
TAGCTTCTTA	ATAGGAACCT	GGGGGTGGGT	3780
ATCGGTTTTG	TTTTTGTTTT	TGTTTTTTCC	3840
ACTGTTTTCC	TCCCTAAGGG	TTGAGAGCCC	3900
TACCCCAGGG	CCTTTGCACA	TGGAGTCCCA	3960
CTTACTGCAT	TTGGCTCTTG	GTAAGTGTCC	4020
CCCAGCTCCC	TCTCTTCTCC	TCCCCCCTTT	4080
TTTTTCTTTT	TGGCTTTTTG	AGACAGGGTT	4140
CATTCTGTAG	ACCAGGCTAG	CCTCAAATCTC	4200
CTGGCACTAA	AGATGTGGGC	CACCACAACCT	4260
CCTATAGTGA	CCTCAGTTCC	TGGCATATTG	4320

Fig.3(viii)

SUBSTITUTE SHEET (RULE 26)

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TAGGCGATGG	ATGGATGAAT	GGATGGATGG
CTTGAATCGT	CCTGAGTGAA	AAAAGAGACC
GGCAGCCTGG	CCTGCTGGTC	TCATGGGAGC
CACCCTGCCA	TCCTGTGTGG	CTGACAAGAA
AGGGAAGCTT	GGAATATGTT	CCCCTCCTCA
CCAGCCTATG	AGTAGGGCAG	CTGTGGGCTG
GTCCCTCAGG	GTGGGTCACA	GGATTGAGGT
AGGAAATGAT	TGTGGAGAGT	CAGAACTCCT
GCTTCTGTGG	CTGTCCCTTC	TCTTGTGGTC
TGTGAGGAGG	GCACGGGGAA	AATGAAGGCT
CCAACAGGGC	TCACCTCTCC	TCTGGACAGG
TTTGATTCCC	TTCCTTTGGT	CTCCTGGGAT
TTTTAGATAT	GTCCATTCTC	CAGAAACACA
ACCACCAGGA	CAGACAAAGA	ATTGGAGAGG
TGGCTTATGT	GTAATCCCAG	AACTCTGGAC
CAGTGTGTTC	TAGGTAATGA	GACCCTGTCA
ATGTTTATAG	GCTGTGAGAC	AGCTTGGTGG
CCTCAGCCCC	ATCCCTAGGA	ATCCATGGTA

Fig.3(ix)

SUBSTITUTE SHEET (RULE 26)

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ATGGATGGAT	GGATGGTTGG	ATGGAGCAAG	4380
TCAGAGAACT	GAATGGAGTT	AGGTTCCCAG	4440
TCCCTGTGAA	ACTTCCCCCA	CACCTCCCAC	4500
AGGCCAATGG	CCAGATGGGG	ACACAGACTC	4560
TATCCTAGGC	CTTGTTGTCC	CCCTGAGGGC	4620
CCCTAAGGTT	GGGTAGGCAA	GAAGGGGGTG	4680
CATTTCCAAA	GTGGCCATCA	CAGTGGCCCT	4740
GTTGGGAGTT	GTAGAGGGCC	TTGCATGTGG	4800
CTTTGCACAG	TCCCCTCGTG	TGTGCTGGGA	4860
CAGCCCCTCA	GCTTGCCCTT	CACGGTTCAC	4920
CTCTCACTGT	ATGCACAGAT	TGGCCTCACA	4980
GACAAACATT	TACCAGGGTA	GGATTTTACA	5040
CTTGTGAGGT	TAGGGTATCA	GTGAAAGGAC	5100
AAGGAAATTG	GTAAGCCAGG	CCATGCTTGA	5160
GCTGAGGCAG	GAGGATTCCA	AGTTTCAAGA	5220
AGAAAAGAAA	AGAAATAAAG	AGACAAGAAA	5280
GTAAGGGGCA	CTTGCCTCCA	ATCAAGATGA	5340
GAAGGAGAAA	GCAAACCTCCA	GCTGCTGACC	5400

Fig.3(x)

SUBSTITUTE SHEET (RULE 26)

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TCCATACATG	TGCTCCAATG	TGCACACACA
TTTGCTTAGA	TTTGAGTAGG	CATTTATGAC
GAAAATATAC	CTGTTTGTAT	TTGGTTTGGT
GCTTCTCTGT	GTAGTCCTGG	CTGTCCTTGG
ACTCAGAAAT	CCGCCTGCTT	GTGCTTCCCA
TCAGCAAAAT	TGCATACTTT	AACCCCAGTA
ATTCCAGGCT	AGCCAAGGAT	ACAGAGTGAG
CCAAAATGTA	TTTTGTGCTT	GTGTATGTAC
ACAACCTTGTA	GAAGTTCTCT	CCGTTACACAG
AGGCTTAGCC	ACAGTCTTCT	TTATGTACTG
GAATTAATTT	TTGAGATAAG	GTCTCTTGTA
AAGGTCATCT	TGAGCTGCTG	GTACTCTTGC
GCAGCACTTC	TCTGGGGAAG	GGGCTGGCCT
GAGTGCTTGG	GTCTCGTTGT	TTCTTTTCTT
GACTTCCTGA	CTCTTGAAAC	ATCCAGGCAG
GCCTAACAAA	GTGTCGTCTT	TGACCCCAGA
CCTTCTCATC	GGCTCCTCCC	TGCAAGCTAC
CACCGCTGAG	GGGCTCTACT	GGACCTTCAA

Fig.3(xi)

SUBSTITUTE SHEET (RULE 26)

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CAGGGAGACA	TAATCAATTA	ATAGGATGTA	5460
TGATGTTTTA	AAATTTTTTAT	TTGATTTTTAT	5520
TTGGTTTGAG	TTTTGTTTAT	TTGAGACAGG	5580
AACTCACTCT	GTAGACCAGG	CTGGCCTTGA	5640
AGTGCTTAGA	TTAAAGGTGT	GCACTGCCAT	5700
TTTGGGAGGC	AGAGGCAGAC	TAATGTGTGA	5760
ACCCTATTCT	TACCCTCCCC	CCCCAAAACC	5820
ATGTGTGTTG	CAGCACGTAA	ATGTCCAAGG	5880
TCTAAGTCCT	GAATTCAAAC	TAAGGTCCTC	5940
AGCCATTTCA	CTGGCCCTGG	ATTGACTGAT	6000
GCTCTAGCTA	GGCTCAAAC	ATGAACTCCC	6060
TTCCACCCCA	AGTGGTGGAA	TGATACTCAG	6120
TGGCCTTGAT	TTTGTTGCCT	CAGCTTCAAT	6180
TATCTGTGAA	ATGGGTGAAC	ACCTGTTCAA	6240
GGTGAGGGAC	TTGAAGTGGG	CTCATCCCAT	6300
CACAGCTGTA	ATCAGCCCCC	AGGACCCCAC	6360
CTGCTCTATA	CATGGAGACA	CACCTGGGGC	6420
TGGTCGCCGC	CTGCCCTCTG	AGCTGTCCCG	6480

Fig.3(xii)

SUBSTITUTE SHEET (RULE 26)

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CCTCCTTAAC	ACCTCCACCC	TGGCCCTGGC
GTCAGGAGAC	AATCTGGTGT	GTCACGCCCCG
CTATGTTGGC	TGTAAGTGGG	GCCCCAGACA
GATTTAGAGC	CTGGGTCTTC	TGTCCTGGGG
CATGGTCATA	CCCAGCACAG	GCATTGCAAC
TGTGTACCCC	ACAGCTTTAG	AAAAGCTGTC
CCTTTAACAT	CAGCTGCTGG	TCCCGGAACA
GTGCACACGG	GGAGACATTC	TTACATACCA
TACCCAGCCA	AGCCTTGCTG	TGTGACTTCT
TTCCTGTTTA	TGAACTCAA	AGGGACTCTC
CACATGTGAG	GAGTACCACA	CTGTGGGCCC
CCTCTTCACT	CCCTATGAGA	TCTGGGTGGA
TGATGTCCTC	ACACTGGATG	TCCTGGACGT
GCCCTAGACC	TTATAGGGCG	CCTCCCCCCC
GTCTTAGCCA	CAGCCACGGT	GGTTGCAGGA
TTTCCCCCAA	GACAGTCAAG	ATTTTCCCCT
CTCTGCAGAG	AACACCTGGC	CTGACCACCC
GAGTCCTAGG	GGACTGAGAG	GAGGCGCCCA

Fig.3(xiii)

33/43

CCTGGCTAAC	CTTAATGGGT	CCAGGCAGCA	6540
AGACGGCAGC	ATTCTGGCTG	GCTCCTGCCT	6600
CTCAGAGATA	GATGGGGGTT	GGCAATGACA	6660
CAGAGCCATG	GGCTCTCACT	TGCATGCAGG	6720
TCTAGGGACA	GCTGTGGCTG	CACTGTCCCC	6780
ATGTTTTTCCT	TGTAGTGCCC	CCTGAGAAGC	6840
TGAAGGATCT	CACGTGCCGC	TGGACACCGG	6900
ACTACTCCCT	CAAGTACAAG	CTGAGGTTGG	6960
GGCAATACTT	ACCTTCTCTG	ATCAAATATG	7020
GCACCTCCAC	AGGTGGTACG	GTCAGGATAA	7080
TCACTCATGC	CATATCCCCA	AGGACCTGGC	7140
AGCCACCAAT	CGCCTAGGCT	CAGCAAGATC	7200
GGGTGAGCCC	CCAGTGTCCA	CCTGTGTTCT	7260
ATCCCCCCAG	ACTTTTTTGGT	TCTTCTAGAG	7320
CAGTGGTTGT	TCATAACTTA	ATGCAAAGAC	7380
CCCCACCCCC	AACACACACA	TACACACACA	7440
TCCCTCTCTA	CAGCCCAGGT	G TTCAGAAGG	7500
GGTCTGAAGG	CGCCCCAGGA	AGCCGAGGCC	7560

Fig.3(xiv)

SUBSTITUTE SHEET (RULE 26)

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TTGAGCTGGG	GGGGGGGGCG	AGGGTTGGAG
GGGCCTAATC	TAATTAGGGT	GTTCCCAGCC
GTGCCTCACT	GAAGACTCAG	GGGAGAGATC
GGGTTCCTGG	GTGCCCCTGG	CTCATTCCCA
TAACCCTCAG	TTGTGCTCTG	TGGCTGGCAC
CAAGGCATCA	GAGGTGGACA	TGGGATGGGG
AAGGTGGGGT	GATATACAAT	AAAGCTTGTC
GATCACAATT	GTTGACATCA	CTCTGGGACA
AGTAGCTTTA	AGAGTCAGCT	TGTGACTTAA
GTGATGCTCG	CCTCACTCCC	TGTTTAGTGA
GTGGGCTGCT	CTGTCCCCTT	GAGGGCAGGA
TGGTAGCAGC	AACTGCTGCT	GGCTGTTTCT
CTGGGTGAGT	AGCTAACAGG	GGTGGGGGCG
AGCCACTGCA	GCCTAGATTA	CACCACTGGG
AGTCCTCAGA	ACTGGGAGCA	CTGTTGCCAG
AGGGGAGGCA	GAGGCAGAAG	GATCTCTCTG
AGCTCCAGGC	CAGCCAGGGT	GCGCAGTAAA
TGACCAGGCT	TGCTCCACCC	CCAGTGACCA

Fig.3(xv)

35/43

GCACGAACTG	GATGATCCCT	GAGCACAACT	7620
CAAAGCAGCC	TGGGCCATTT	AACCCTTCAA	7680
AGCTTGTACT	CTCTCCATGG	TCCCCCAGGA	7740
CATCCAGAGG	TTTTGTGTCT	TCCTGGCATC	7800
AGCTGCCCCG	TGGAGGCTCT	TGGTAATGTA	7860
ATACATAGGG	ATGGAGCCAA	ATAGCACCTC	7920
ACCCTGACGC	TCAGAAAGCC	TACTCATGAT	7980
TGTAGTGAGA	CCCTAGCTCA	AAACACAGAC	8040
TACTGGAACT	CAGGGCCTAA	TAGGTGCTGG	8100
GATCTCTGCG	CTAATCTCCA	CCCCAGCTGG	8160
ATGTGTGTCT	TCCATCAGAG	ATAGGACCCG	8220
GGAATATTAA	ATGACAGTAA	TCTATCAGGC	8280
TGGTCTGGAA	AACGCAGATA	GGGTCATAGG	8340
TGTTCTGTCA	CTAGGCCATT	CTCACCAAGC	8400
CATTTAATGC	CAGCATTTAA	TGCCAGCATT	8460
AGTTCAAGGC	CATCCTGAAT	TTACATAAAG	8520
ACCTTGCTCTC	AAAAAACAAA	GCATCTTTAG	8580
CGGACCCCCC	ACCCGACGTG	CACGTGAGCC	8640

Fig.3(xvi)

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GCGTTGGGGG	CCTGGAGGAC	CAGCTGAGTG
ATTTCCTCTT	CCAAGCCAAG	TACCAGATCC
AGGTGCCCCGT	CCCGCCCCGG	ACCCGCCCCCT
CACCGTGCAG	GTGGTGGATG	ACGTCAGCAA
GCCCGGCACC	GTTTACTTCG	TCCAAGTGCG
AAAGGCGGGA	ATCTGGAGCG	AGTGGAGCCA
TGAGCACCTC	TCCAGGGCTG	GCTGGCCCAT
CCCACCCTTT	TTTTGAGACA	GCGTCTTCAG
TAGTCAAGGA	TGACCTCGAG	CTCCTGGTCT
GGCCATCACC	ACCTTTGGGA	GACTAGCCAT
GATGGAGTAC	AACAGTGTGA	CCTCTTGTA
AATATCCTAG	GCTCTCTAGA	GGTTAACTTT
TCACATGGTC	CCACAGAACC	TTTTGTCACA
CACATAAGGG	TCTCTACTGC	TGGCCCACCC
CTTAATATTT	GCAATCCTCC	TACCTCAGCC
CAAGTTTCTC	TTCTCTGGGT	CCCTTTCTTA
GTCCTGAAGA	CTCTCCGAGC	CCATGGATCT
AATGTCTGGC	CTCAGTTTCC	CCACCTGTCA

Fig.3(xvii)

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TGCGCTGGGT	CTCACCACCA	GCTCTCAAGG	8700
GCTACCGCGT	GGAGGACAGC	GTGGACTGGA	8760
GACCCCGCCC	CCCGCATCTG	ACTCCTCCCT	8820
CCAGACCTCC	TGCCGTCTCG	CGGGCCTGAA	8880
TTGTAACCCA	TCGGGATCT	ATGGGTCGAA	8940
CCCCACCGCT	GCCTCCACCC	CTCGAAGTGG	9000
GGAATCCCCA	ATCCATCCTG	TTCCTTCCCC	9060
GTAGCGCATG	CTGGCCTTAA	ATTCAGTATG	9120
TTTTGTCTCC	ACTTAGAGAC	AATGGCCAGT	9180
GGAGTCTATT	TAGCCTGTCA	TTTGGTGACA	9240
GAGAACTGAA	GACAGGCTGT	TTTTAACCCC	9300
ATATAAAATA	GAGACTATTA	CAGCCAGTTA	9360
CAACCTATAG	ACCACAGTGC	CTGTGCCTAC	9420
CTCCAACCCT	TAAAAGGTAA	CCTAGGCAGC	9480
TCTTGAATGC	TCAGAAACCA	GGCATTAAACC	9540
AGGTGGGAGG	GCCTAAAGAT	GACTTCCTTT	9600
GCACTCTCTA	ATATGAAATA	TATTGCATAA	9660
GGTTTAGGCA	GCACAGTCGG	TCCAAGACAC	9720

Fig.3(xviii)

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TTCATTATTT	GCAGGCAGTA	TAAGAAGAAG
CTAAGACAGA	ATACTTCTAC	ACTGAAACTG
TGATGATGAA	ATAATGGGGA	AACTGAGGCT
ACCAGCTCCA	GGAAGCTCTC	CAGCCCCCAT
GAGTGAACAC	AGCTGGGAGG	GGCTGGAGCC
ACCTGCGATT	CTTGCACGGG	AGCCAGCAGG
CCGGGGGGTAG	GGTTGGAGGG	AGGTAAGCAG
CCTGTCAGCG	AGTCCCCAGT	TTTATTTATG
TGCTGGGGGA	TGGCTGCGGC	TGGGGATTGG
CAGCCCCTC	CATGTCACAC	CCGTGCATTC
TTCTGTGCTG	TCTGTCTCTA	TTTCTGTCAT
TTAATATAAC	TACGTTTTAA	AAATTGCTTT
GTGCCACAAC	ACACACGTGA	AGGTTAGAGA
GGGACTAGGG	CTGGCGACAA	GAGCAATTAC
CTTCCCATCC	TGTTTGGATA	GTCATAGGTA
TAGCTATCCT	GCCTCAGCCT	ACCAAGTGCT
TCCCAGTGTC	TGGGGGTACA	CAGTCCCAAG
TGCCCCTTGC	TTTGTCCGTG	TCCCTAGAGT

Fig.3(xix)

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CTCCCATCCC	CCACCCGCTT	CCTCCGGTCC	9780
AACTCTCGCA	GACGCATATG	CTCACTTTAA	9840
CCGAGAGATT	CCTGGAGGAA	GAGGGTCAAA	9900
CCGGGCCTCT	CCAGGTTCTG	GGCTTGGCGG	9960
TGGGAGCTTT	GGCCCTTGCT	CGTGCCCAGC	10020
CGGCTGCGTC	CGCCCGAGAG	ACTGAAGAAG	10080
GGGCTGTGGG	GGCCGAAGCT	TGTGCCAGGG	10140
GCGTGAGGCC	GATGTCCTTA	TCCGCTGGCC	10200
ACCCAAGGGC	TGGCTTCCCA	CTCAGTCCTC	10260
TCTGAGGCTT	ATCTTGGGAA	CCCGCCCTTG	10320
TCACTTTCCC	AGAGCCTTTT	TTTTATGCTT	10380
TGTATAATGT	GTGTGCCTTC	GTGAGCGTGC	10440
ACTTTGTTGA	GTAGGCTCCT	TCCACCATGT	10500
TGAGTCATCT	CGCCAGCCCC	TCACCCCTCA	10560
ATCGAAGGTA	AATCGCTGGC	TTTAATTTCG	10620
GTGCTACCAC	GTTTGTGGGA	GGGGCTCTCC	10680
ATCTCTGCTT	TCTAGGTCTT	TGTCTTAGTT	10740
CTCCGGCCCC	ACTTAGTCTC	CATTGATTTC	10800

Fig.3(xx)

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CTTTCTGACC	GAATACTCGG	TTTTACCTCC
CCATCGCCGT	GGCATTGCCA	TTCCTCTGGG
CAACTTTCCC	CAGCCGAAGC	TGGTCTGGTA
GCTGGCCGCG	CCCCAACACT	GCCGCTCCAT
GGGTGTGCGA	GCCGCGGGGC	GGCGAGCCCA
AGTTCCTCGG	CTGGCTCAAG	AAGCACGCAT
ACCAGTGGCG	TGCTTGGATG	CAGAAGTCAC
GGGAGGCTTG	CGTGGGGGGT	AAAGGAGCAG
CACAACACCG	CACTCTTCTT	TCCAAGCACA
GGGTGCGGCG	AGAGGTAAGG	GGGTCTGGGT
CCTTTCCCCT	CCTTCGGTGT	TGCTCAAAGG
AAGAGCCCCA	GGTTTTACTG	CATCATCAAG
CTTTTCTGCC	CTCAGGTCCT	GCCGGCTAAA
CAGACCTGGA	GGCTCACCTG	AATTGGAGCC
TACCAGAGGC	TGGGCACAAT	GAGCTCCCAC
ACTTGGATAT	ACCCAGTGT	GGGTAGGGTT
TTAAATAAAT	AAAGGAGTTG	TTCAGGTCCC
GGGGTGGGGG	GA	

Fig.3(xxi)

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CACTGATTTG	ACTCCCTCCT	TTGCTTGTCT	10860
TGACTCTGGG	TCCACACCTG	ACACCTTTCC	10920
TGGGAGGCCG	CCGTCCCGCG	CGCGCCTCCT	10980
TCTCTTTAGA	GCGCCCGGGC	CCGGGCGGCG	11040
GCTCGGGCCC	GGTGCGGCGC	GAGCTCAAGC	11100
ACTGCTCGAA	CCTTAGTTTC	CGCCTGTACG	11160
ACAAGACCCG	AAACCAGGTA	GGAAAGTTGG	11220
AGGAAGAGAG	AGACCCGGGT	GAGCAGCCTC	11280
GGACGAGGGG	ATCCTGCCCT	CGGGCAGACG	11340
GAGTGGGGCC	TACAGCAGTC	TAGATGAGGC	11400
GATCTCTTAG	TGCTCATTTTC	ACCCACTGCA	11460
TTGCTGAAGG	GTCCAGGCTT	AATGTGGCCT	11520
CTCTAAGGAT	AGGCCATCCT	CCTGCTGGGT	11580
CCTCTGTACC	ATCTGGGCAA	CAAAGAAACC	11640
AACCACAGCT	TTGGTCCACA	TGATGGTCAC	11700
GGGGTATTGC	AGGGCCTCCC	AAGAGTCTCT	11760
GATGGCCAGT	GTGTTTGGGG	CCTATGTGCT	11820
			11832

Fig.3(xxii)

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MURINE NR-6 GENOMIC STRUCTURE

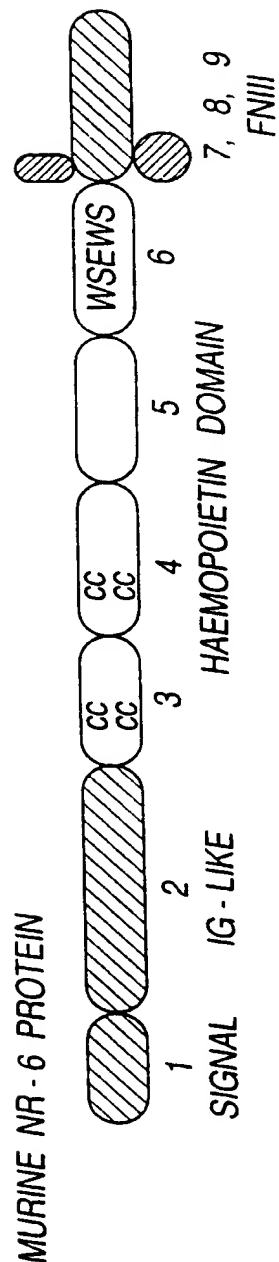
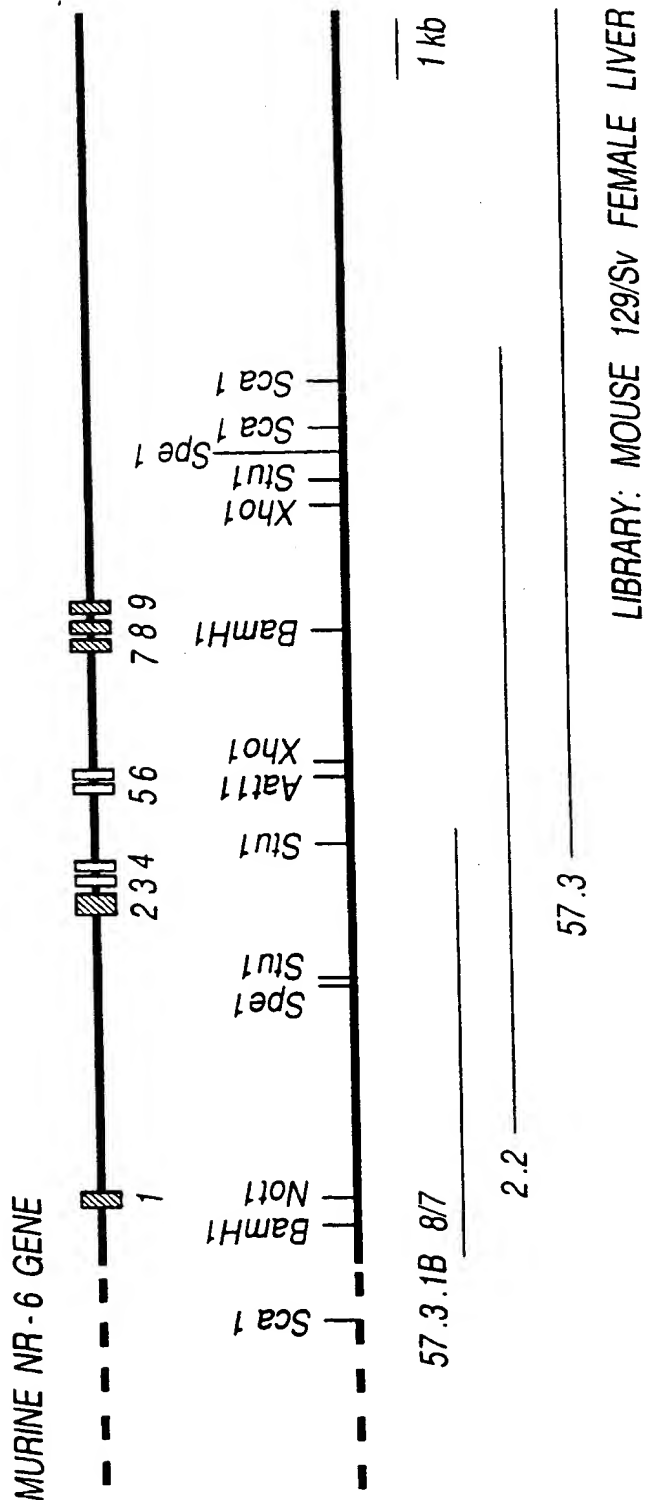


Fig.4

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TARGETING THE NR6 LOCUS BY HOMOLOGOUS RECOMBINATION

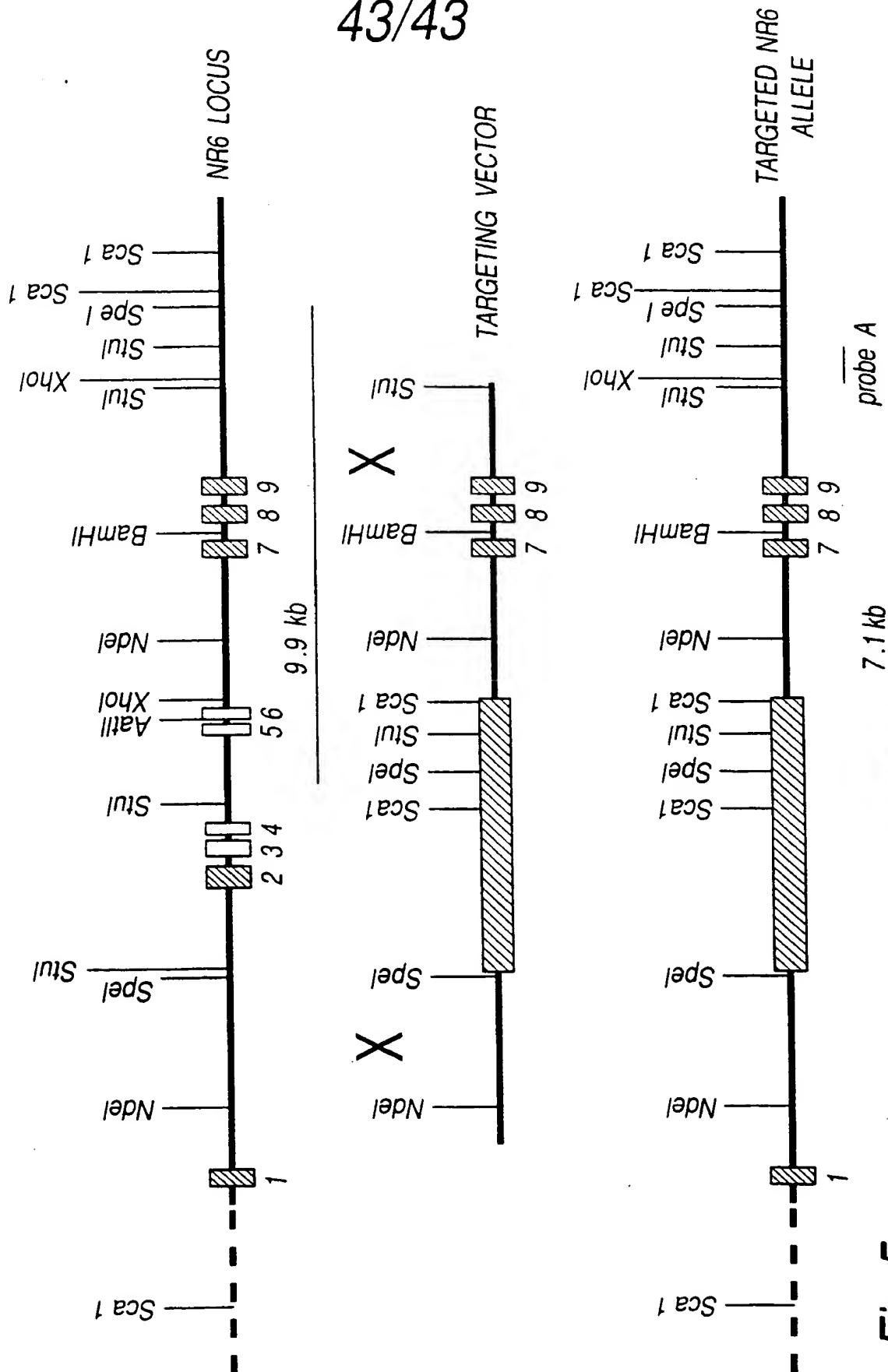


Fig.5

INTERNATIONAL SEARCH REPORT

Internatic Application No
PCT/GB 97/02479

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/19 C07K14/715 A61K38/17 C07K16/18 A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE EMEST12 embl SEQ ID MM77631 Acc.No:W66776, 15 June 1996 "Mus musculus cDNA mel7b11.r1 similar to PIR:B38252 granulocyte colony-stimulating factor receptor precursor" XP002055540 cited in the application & MARRA ET AL.: "The Wahu-HHMI mouse EST project"</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	<p>1-10, 14-19</p>

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

12 February 1998

Date of mailing of the international search report

06.03.98

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INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/GB 97/02479

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ROBB ET AL.: "Structural analysis of the gene encoding the murine Interleukin-11 receptor alpha-chain and a related locus" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 271, no. 23, 7 June 1996, MD US, pages 13754-13761, XP002055539 see figure 3 ---	1-3,20, 21
X	WO 96 08510 A (PROGENITOR, INC.) 21 March 1996 see figure 2c nucleotides 1053-1068 on sheet 4/11 ---	1-3,20, 21
X	WO 96 07737 A (AMRAD OPERATIONS PTY. LTD.) 14 March 1996 see figure 8 nucleotides 1040-1055 on sheet 14/21 see claims 1,13 ---	1,3,13, 20
P,X	WO 97 15663 A (AMRAD OPERATIONS PTY. LTD.) 1 May 1997 see figure 7 (vii) on sheet 20/24 ---	1-3,20, 21
P,X	WO 97 12037 A (AMRAD OPERATIONS PTY. LTD.) 3 April 1997 see claims 1-3 ---	1-3,20, 21
P,X	WO 97 25425 A (GENENTECH, INC.) 17 July 1997 see figure 2b on sheet 12/85 -----	1-3,20, 21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 97/02479

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 97/02479

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Remark : Although claims 28 and 29 are directed to a method of treatment of the human/animal body , the search has been carried out and based on the alleged effects of the composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 97/02479

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9608510 A	21-03-96	US 5643748 A AU 3419495 A CA 2176463 A EP 0730606 A	01-07-97 29-03-96 21-03-96 11-09-96
WO 9607737 A	14-03-96	AU 3465295 A CA 2197873 A EP 0804576 A	27-03-96 14-03-96 05-11-97
WO 9715663 A	01-05-97	AU 7266896 A	15-05-97
WO 9712037 A	03-04-97	AU 6980596 A	17-04-97
WO 9725425 A	17-07-97	AU 1574797 A	01-08-97